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GRAVE SEQUELAE OF BLOOD TRANSFUSIONS; A CLINICAL STUDY OF 13 CASES OCCURRING IN 3500 BLOOD TRANSFUSIONS *

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By the year 1910, the contributions to our knowledge of isohemagglutination made by Landsteiner, Shattock, Hektoen, Janský, Moss, and others had laid the foundation for a great reduction in mortality from the transfusion of blood. The introduction of citrated blood by Agote, Weil, and Lewisohn during the World War, provided a much simpler method than had been in previous use. As a result of the reduction in hazards and the increase in technical facility, blood transfusion has become a common therapeutic procedure. The ease of administration and the relatively small mortality have unfortunately impressed many operators only with the innocuousness of the treatment. Despite the warnings of many writers, it must be true that serious complications have frequently occurred but have not received proper notice in the medical literature. A survey of recent publications on blood transfusion reactions indicates that interest in the subject is being reawakened.

The reactions following blood transfusion have been variously classified. Polayes and Lederer [1] have published an excellent review of the subject. Because of the lack of knowledge of the exact mechanisms involved, any etiological classification at present must necessarily contain potential errors. In this paper the various allergic manifestations, febrile reactions, and the transmission of disease will be ignored. The serious reactions which result in jeopardy of life or in permanent damage will be considered and illustrated with appropriate cases from our experience.

From November 1933 to July 1937, approximately 3,500 blood transfusions were performed in the University Hospitals of the State University of Iowa. Citrated blood was utilized almost exclusively. It was administered through small needles by gravity. All serious complications result-

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ing from transfusion were studied as thoroughly as circumstances permitted. All transfusions were administered by the interns under supervision of the resident staff. No "transfusion teams" were utilized. The hospital maintained a donor list consisting mostly of the resident staff, interns, nurses, employees, and medical students. Beginning July 1, 1936, a physician in the bacteriology laboratory was made responsible for the determination of the blood groups of all donors and recipients except in the case of some emergencies. The interns performed the cross-matching of donors' and recipients' bloods under supervision. Most of the transfusions were given with bloods of the same group although bloods of Group O were occasionally used when the homologous group was not available.

Renal Insufficiency from Blood Transfusion

The syndrome of uremia with oliguria or anuria has long been known to occur, not only in hemolytic transfusion reactions but also in blackwater fever and in hemoglobinemia caused by various drugs such as quinine [2] and phenylhydrazine. The mechanism has been variously explained. Bordley [3] discussed four theories which had been proposed: 1. Baker and Dodds [4] suggested that the renal tubules become blocked by hemoglobin pigment precipitating in an acid solution. They produced the condition in rabbits and this work has been recently confirmed experimentally in dogs by DeGowin, Osterhagen, and Andersch.[5] The principal objection to this theory is that in many human cases not enough pathologic evidence of tubular obstruction can be found. 2. The renal lesions are the result of loss of chlorides similar to the cases described by Brown et al.[6] Chemical study of many cases does not justify this explanation. 3. Longcope and Rackemann [7] described cases with urticaria which developed renal insufficiency. It has been suggested that this mechanism might be involved in transfusion anuria. This is difficult to disprove save that the clinical syndrome can be reproduced in dogs with a single transfusion.[5] 4. A nephrotoxic substance is released by hemolysis. This has no experimental proof at present. A fifth explanation has been introduced by the work of Mason and Mann [8] and Hesse and Filatov [9] which demonstrated a vasoconstrictor action of hemoglobin on the kidney. Hesse and Filatov believe that the renal damage is due to ischemia. The experimental work of the latter workers requires confirmation.

Most writers have agreed that the renal insufficiency following blood transfusion is dependent on hemolysis resulting from the administration of incompatible blood. Whether there is an alternative explanation in some cases remains to be proved. Cases of transfusion anuria have been reported where no incompatibility of bloods could be demonstrated by the usual laboratory methods and in which hemoglobinuria was not noted.[10, 11, 12] Failure to demonstrate incompatibility in these cases can scarcely be ascribed to faulty technic as all of these tests were checked subsequent to the transfusion reactions, a situation which naturally constituted a stimulus to careful

work. A more plausible interpretation is that for a small number of bloods our present laboratory methods are inadequate to detect all incompatibilities. The absence of hemoglobinuria and jaundice does not constitute unequivocal evidence that hemolysis did not occur. Lichty, Havill, and Whipple [13] have shown that there is a renal threshold for hemoglobin, and Drabkin, Widerman, and Landow [14] have calculated that only about 10 per cent of the hemoglobin disappearing from the blood plasma is excreted in the urine. Two of our cases had hemoglobinemia two hours after transfusion reactions but in neither could hemoglobin be detected in the urine.

Undoubtedly the most common cause of the transfusion of incompatible blood is still the occurrence of gross errors in the preliminary cross-matching. It is difficult to conceive of any laboratory procedure in which an error can directly cause more disastrous results to the patient than in blood matching and blood grouping. Yet conversation with many interns graduated from various recognized medical schools reveals that they have only a very rudimentary and fragmentary knowledge of all procedures pertaining to the determination of blood incompatibility, transfusion technic, and transfusion reactions. In fact, a survey of the standard textbooks on laboratory diagnosis demonstrates that many of the presentations of the subject are inadequate reflections of our present knowledge. It has become necessary in this hospital to give lectures and laboratory demonstrations to each new class of interns.

Case Reports

Case 1.[15] E. A., a 53 year old woman, had hemorrhages from the colon, probably as a result of roentgen irradiation for adenocarcinoma of the cervix uteri. Her blood was classified as Group O. In October 1931, she received transfusions from two Group O donors without reaction. In October and November 1933, three transfusions were given from different Group O donors with a febrile reaction following each. Preliminary cross-matchings by the hanging-drop method revealed no incompatibilities. The last transfusion was made with washed erythrocytes only. Immediately after transfusion she complained of severe pain in the neck, thighs, and abdomen. This was followed by a chill and the temperature rose to 103.2° F. per rectum. Jaundice was evident within seven hours. The urine was diminished in volume and contained hemoglobin and granular pigment casts. The patient continued to vomit; she became drowsy and generalized edema developed. Death in coma occurred ten days after the transfusion. Permission for autopsy was refused. After the reaction had occurred the donor's and the recipient's bloods were re-typed and cross-matched. They were found to belong to Group O and no agglutination could be observed. There was some hemolysis of the donor's corpuscles by the recipient's serum, however. It is possible that more suitable laboratory methods might have demonstrated the incompatibility more satisfactorily.

Treatment: Intravenous injections of isotonic saline and hypertonic dextrose solutions; diathermy to the kidney regions; irrigation of the renal pelves with hot water; phlebotomy with withdrawal of 200 c.c. of blood.

Blood chemical studies shown in table on top of page 1780.

Case 2.[15] W. B., a 65 year old man, had bleeding from a duodenal ulcer. His blood was classified as Group O. During November 1933, he received two transfusions from donors who were supposed to belong to Group O. Preliminary cross-

Date 1933	van den Bergh	Blood Urea Nitrogen mg. %	Blood Uric Acid mg. %	Blood Creatinine mg. %	CO_2 Combining Power vol. %	Plasma Chlorides mg. %
November 1	4.4 indirect					
November 12		Transfusion				
November 13	17.4 direct					
November 14	0.9 direct	79.4	6.6	4.0	35.0	
November 15	0.9 direct	86.8	6.6	7.7	34.1	536
November 17		91.9	6.8	10.0		
November 19		94.5		12.0	26.8	555
November 20		100.0	10.0	11.5		
November 21		102.0	9.6	12.0	24.0	555
November 22		Died				

matching by the hanging-drop method revealed no incompatibilities. There was no reaction after the first transfusion. During the second transfusion, after 75 c.c. of blood had been given, the patient complained of a cramp in the thigh. A total of 500 c.c. of blood was given. One hour afterward he became nauseated and vomited; a slight chill was followed by a temperature of 100.4° F. per rectum. Complete anuria developed. No jaundice was detected but examination of the blood plasma was not made until two days after transfusion. The patient continued to vomit, gradually become stuporous and died in coma 10 days after transfusion. Cross-matching of the recipient's blood with that of the last donor by the hanging-drop method revealed no incompatibility. Three years later, the donor's blood was typed with sera of high titer and found to belong to Group A. The donor stated that he had given eight transfusions as a Group O without reactions.

Treatment: Isotonic saline intravenously and by hypodermoclysis; hypertonic dextrose intravenously; irrigation of the renal pelves with hot water.

Autopsy: The pathologist reported the significant lesions to be central necrosis of the liver lobules and necrosis of the tubular epithelium of the kidneys with some plugging of the lumina with debris and pigment.

Blood chemical studies:

Date 1933	Blood Urea Nitrogen mg. %	Blood Uric Acid mg. %	Blood Creatinine mg. %	CO_2 Combining Power vol. %	Plasma Chlorides mg. %	van den Bergh
November 10	14.0	3.1	1.0	58.7	602	
November 25			Transfusion			
November 27	62.3	5.5	6.4	58.9	600	
November 28	80.5	6.5	8.3	56.0	595	0.2 indirect
November 29	88.9	8.5	10.7			
December 1	125.0	10.0	13.0	45.7	585	
December 2	141.4	10.0	15.5	35.2		
December 4	164.0	10.0	14.0	31.5		
December 5	193.4	10.0	17.6			
			Died			

Case 3. A. Z., a 57 year old man, was admitted to the hospital November 28, 1934, in semi-coma. He had been known to have pernicious anemia for four years.

He was pale, disoriented, and afebrile. Extensive retinal hemorrhages were present. The blood pressure was systolic 125 and diastolic 75 mm. of mercury. The urine contained some albumin, erythrocytes, and a few coarse casts composed of brownish pigment. Hemoglobin 38 per cent (Sahli); erythrocytes 1,650,000 and leukocytes 23,450 per cu. mm.; reticulocytes 17 per cent. The patient vomited frequently and developed edema of the ankles. The urinary volume for three days was 850 c.c. He died in coma three days after admission.

Blood chemical studies:

Date 1934	Blood Urea Nitrogen mg. %	Blood Uric Acid mg. %	Blood Creatinine mg. %	CO_2 Combining Power vol. %	Plasma Chlorides mg. %	van den Bergh
November 28	144.9	23.2	14.3			0.9 direct
November 30	155.4	18.5	12.3	25.8	587	0.8 direct

Treatment: Isotonic saline and hypertonic dextrose solutions intravenously.

Autopsy: The following anatomic diagnoses were made: hyperplasia of the bone marrow, hemosiderosis of the liver and spleen, slight chronic gastritis, degeneration of the posterior columns of the spinal cord, acute tubular nephritis (blood transfusion reaction), acute cholecystitis, acute myocarditis, passive congestion of the lungs, bilateral pleural effusion, old hemorrhages of cerebellum, polyp of sigmoid colon, emphysematous cystitis.

The pathologist was the first to suggest that the patient had died from a blood transfusion reaction. Subsequent correspondence with the referring physician revealed that on November 20 the patient had received 300 c.c. of whole blood from a type O donor. This was immediately followed by a severe chill and an oral temperature of 100.8° F. On November 23 he had received another transfusion of 250 c.c. of blood which was followed by a chill. Death, then, occurred 10 days after the first transfusion.

Case 4. A. P., a 57 year old man, was admitted to the hospital December 31, 1934, with severe bilateral pyelonephritis, chronic cystitis, benign hyperplasia of the prostate, and bilateral ureteritis. An indwelling urethral catheter was placed and he was given ammonium nitrate, 1.4 grams (gr. 22½) thrice daily, and serenium, five grains thrice daily. His blood was classified as Group O and was apparently compatible with that of the donor whose blood produced the fatal reaction in Case 2. On January 8, 250 c.c. of this donor's blood had been given to the recipient when the transfusion was discontinued because the patient developed a severe chill and oral temperature of 105.2° F. Anuria promptly developed. Vomiting and stupor intervened. On January 12 the condition was desperate. There was some edema of the lungs. In spite of that, it was thought that some risk should be taken in an effort to start urinary excretion. Thirty milligrams acetyl β methylcholine were given intravenously. The patient suddenly became much more dyspneic, apparently from increasing pulmonary edema. Atropine sulphate 0.13 mg. (gr. 1/50) was given intravenously with some relief of dyspnea for about two hours but then the extreme dyspnea recurred and the patient died (four days after transfusion).

The bloods of recipient and donor were again cross-matched by the hanging-drop method and no incompatibility was noted. As was reported in Case 2, the donor was proved three years later to belong to Group A when sera of high titer were used.

Treatment: Isotonic saline and hypertonic dextrose solutions intravenously;

roentgen irradiation of the kidney regions; acetyl β methylcholine. Autopsy revealed advanced pyelonephritis.

Blood chemical studies:

Date 1935	Blood Urea Nitrogen mg. %	Blood Creatinine mg. %
January 2	43.4	5.8
January 5	48.3	6.0
January 8	53.9	5.4 Transfusion
January 9	74.2	8.1
January 10	83.3	9.3
January 11	101.5	11.0
January 12	105.7	11.4 Death

Case 5. E. S., a 50 year old woman, was admitted to the hospital with chronic glomerular nephritis. She was pale and slightly edematous. The retinae were normal except for arteriosclerosis. The area of cardiac dullness was somewhat enlarged. Blood pressure systolic 170 and diastolic 100 mm. of mercury. There was gross hematuria and moderate albuminuria. Hemoglobin 30 per cent (Sahli); erythrocytes 2,020,000, and leukocytes 8,400 per cu. mm. The patient's blood was classified as Group A. On May 2, 1935, she was given 500 c.c. of citrated blood from a Group A donor without reaction. On May 6, another Group A donor gave her 500 c.c. citrated blood after preliminary cross-matching. During the administration of the last 50 c.c. she complained of some abdominal pain. Fifteen minutes later she had a chill and the rectal temperature was 104° F. The next day slight jaundice was noted. The urinary excretion became diminished and the hematuria continued until May 15 when the blood completely disappeared from the urine for the first time during hospitalization. There had been some vomiting since admission but on May 18 this became worse and she became comatose and dyspneic. Peripheral edema developed and the ophthalmologists noted papilledema and retinal hemorrhages. She died May 22, sixteen days after the transfusion.

The donor's and recipient's bloods were retyped and both were found to belong to Group A. However, the recipient's serum agglutinated and hemolyzed the donor's corpuscles as well as the corpuscles of an undoubted Group O. These reactions were evident both by the hanging-drop method and by the macroscopic method using small test tubes.

Treatment: Hypertonic saline and dextrose intravenously, sodium bicarbonate intravenously, caffeine citrate intramuscularly, salyrgan intravenously.

Blood chemical studies shown in table on top of page 1783.

Autopsy: Permission was granted only for examination of the kidneys. These showed a typical picture of an actively progressive diffuse nephritis with hemosiderosis of some of the tubular epithelium.

Case 6. A. E., a woman, 46 years old, entered the hospital with vaginal hemorrhage from a uterine fibroid. Hemoglobin 50 per cent (Sahli), erythrocytes 2,000,000 and leukocytes 11,000 per cu. mm. Her blood was classified as Group A and, after preliminary cross-matching, she was given 500 c.c. of citrated blood from a Group A donor (Dr. H.) on July 7, 1936. A half hour later she had chills and the oral temperature rose to 104.2° F. There was considerable vomiting and an increase in amount of vaginal hemorrhage. On July 8 she received 550 c.c. citrated blood from her husband (Mr. E.) whose blood was typed as Group A and seemed compatible by cross-matching. The blood was given at 10 a.m. and was followed by some vomiting but no fever. In the late afternoon jaundice and oliguria were noted. The significance of the oliguria was difficult to evaluate because of the excessive out-

Date 1935	van den Bergh	Blood Urea Nitrogen mg. %	Blood Uric Acid mg. %	Blood Creatinine mg. %	CO_2 Combining Power vol. %	Plasma Chlorides mg. %
April 1		25.9		2.0		
April 5		30.8		2.9		
April 10		22.4	7.6	3.0		
April 15		26.6	7.2	2.5		
April 19		22.4	7.0	3.0		
May 2		21.0	5.1	2.5		
		Transfusion				
May 6		Transfusion				
May 8	2.8 indirect	57.4	6.6	6.5	40.9	625
May 9	3.2 biphasic	62.3	6.2	6.2		
May 10	2.1 biphasic	63.7	7.2	6.2		
May 11	2.4 biphasic	64.4	7.7	6.6		
May 12	2.2 direct	71.4		7.3		
May 13	2.3 direct	68.6	10.2	7.0		
May 14		64.4	11.4	7.4		
May 15	3.7 direct	62.3	10.0	7.7		
May 16	3.0 direct	65.0	11.4	8.1	39.0	625
May 17		65.1	10.6	7.4		
May 18		64.4	10.4	7.7		
May 22	3.5 direct	130.2	15.0	10.3	(Postmortem blood)	
		Died				

side temperature at the time. On July 11 the urinary excretion increased and, subjectively, the patient was better. She received another transfusion from a Group A donor July 12. This was followed by a chill and oral temperature of 103° F. There were no subsequent symptoms, however. On July 22, she received another transfusion from a sister (Group A) with no reaction. On July 27 a transfusion from another Group A donor (Dr. S.) was well tolerated. Vaginal myomectomy was performed July 27 and the patient made an uneventful recovery.

The bloods concerned in the reaction resulting in renal insufficiency were the patient's and those of the donors, Dr. H. and Mr. E. All of these bloods were retyped with sera of high titer and found to belong to Group A. The serum and corpuscles of each were cross-matched with all the others using the hanging-drop, the Vincent open slide method, and the Landsteiner centrifuge method. By none of these tests was any incompatibility ever shown. The possibility that distilled water instead of isotonic saline was added to the blood before transfusion was considered but could not be investigated directly. The stock solutions were tested and no errors in labelling were found.

Blood chemical studies shown in table on top of page 1784.

Treatment: Isotonic saline and hypertonic dextrose intravenously, blood transfusion, spinal anesthesia with procaine hydrochloride. Which of the first two transfusions produced the renal insufficiency is not known. The diuresis and fall in blood urea nitrogen were not prompt enough to be attributed to either transfusion or to the spinal anesthesia. It is the opinion of the clinicians in charge of the case that recovery was spontaneous.

Case 7. D. B., a 28 year old man, had a spastic torticollis following trauma to the head. His blood was classified as Group O. On June 17, 1936, an exploratory craniotomy was performed under avertin anesthesia. During the operation, shock developed and 450 c.c. citrated blood of Group O were administered in the operating room. Chills developed after he was returned to the ward. Another transfusion

Date 1936	Fluid Intake c.c.	Emesis c.c.	Urine c.c.	Blood				
				van den Bergh	Urea Nitrogen mg. %	Uric Acid mg. %	Creatinine mg. %	
July 7	1000	2050						Transfusion
July 8	3800	0	40	7.7 biphasic	53.9	6.8	3.4	Transfusion
July 9	2900	1375	619		67.9	7.0	5.0	Spinal anesthesia
July 10	3200	460	390	3.5 direct	73.5	8.0	5.0	
July 11	3400	225	1550		66.5		5.8	
July 12	2750	50	3400					Transfusion
July 13	4500	50	3635		62.3		5.0	
July 14	4800	0	2800	2.3 direct	56.7	5.6	3.2	
July 15	4500	0	1675		41.3	5.1	3.1	
July 16	3900	0	3425		24.5			
July 17	3500	0	2150					
July 20					9.8	2.8	1.2	
July 22								Transfusion
July 27								Transfusion

was given in the late afternoon and was followed by chills and rectal temperature of 105.8° F. The patient was unable to void. During the next three days he vomited and hiccoughed considerably. Another transfusion was given with Group O blood on June 19. The bloods seemed to be compatible on cross-matching. On June 20 he was still anuric and another transfusion was given. There was a sudden circulatory collapse which temporarily improved after the administration of epinephrine. The patient died three hours after the last transfusion (three days after operation). Just before death, a blood specimen showed the following: blood urea nitrogen 119.0 mg. per cent; blood uric acid 8.0 mg. per cent; blood creatinine 8.7 mg. per cent; CO_2 combining power 23 vol. per cent; plasma chlorides 600 mg. per cent. Treatment: As the anuria was not recognized during life, no specific treatment was given. It seems probable, however, that the patient received some compatible blood after the reaction had occurred.

Autopsy: Anatomic diagnoses: Recent left partial cerebro-frontal lobectomy, intracranial hemorrhage, intraventricular hemorrhage, fatty metamorphosis of the liver with central degeneration, lobular pneumonia and edema of the lungs, acute gastric erosions, mild tubular nephritis (some hemoglobin pigment casts present).

The pathologist first made the diagnosis of transfusion anuria.

The treatment of renal insufficiency following blood transfusion reactions has been extensively discussed in the literature. The clinical course is such that the condition could be recognized in time to apply specific treatment were any known. Many procedures have been proposed and have been reported as successful in isolated cases: intravenous fluids both isotonic and hypertonic; diathermy and roentgen irradiation of the kidney regions; irrigation of the renal pelves with hot water; phlebotomy [16]; intravenous sodium bicarbonate; spinal anesthesia [17]; decapsulation of the kidneys [18]; and transfusions of compatible blood.[19] It is notable, however, that some cases recover spontaneously while others die in spite of the therapeutic measures advocated.

Whether alkalinization of the urine prior to the transfusion will protect the kidneys from the excreted hemoglobin, if hemolysis occurs, is very difficult to prove statistically, because of the small incidence of such hemolytic reactions in any series. Baker and Dodds [4] have shown that such a procedure protects rabbits, and DeGowin, Osterhagen, and Andersch [5] have shown the same for dogs. It must be emphasized, however, that there are certain chemical differences between the blood of most animals and human blood which may complicate the application of this work to clinical practice. In the present state of our knowledge, however, alkalinization of the urine of the recipient before transfusion would seem a desirable precaution.

Tabulation of the treatment received in our seven cases developing renal insufficiency from transfusion reactions would seem to leave much to be desired in therapeutic efficacy. In none of these cases was decapsulation of the kidneys attempted.

Treatment of Transfusion Anuria

Treatment	Case Numbers						
	1	2	3	4	5	6	7
Isotonic saline intravenously	x	x	x	x	x	x	x
Hypertonic dextrose intravenously	x	x	x	x	x	x	x
Sodium bicarbonate intravenously					x		
Diathermy to the kidney regions	x						
Roentgen irradiation of the kidneys				x			
Irrigation of the renal pelves	x	x					
Spinal anesthesia						x	
Phlebotomy	x						
Acetyl β methylcholine				x			
Caffeine citrate intramuscularly					x		
Salyrgan intravenously					x		
Blood transfusion						x	x
Clinical data							
Maximum blood urea nitrogen mg. %	102.0	183.4	155.4	105.7	71.4	73.5	119.0
Maximum blood creatinine mg. %	12.0	17.6	12.3	11.4	11.4	5.8	8.7
Termination	Death	Death	Death	Death	Death	Recovery	Death

Hemolytic Reactions without Renal Insufficiency

It is well recognized that all cases showing hemolysis from blood transfusions do not develop renal insufficiency. Under certain conditions which are not understood, the liberated hemoglobin is taken up by the tissues and a small amount is excreted through the kidneys without apparent harm.

Case Reports

Case 8.[20] E. H., a 25 year old woman, developed postpartum fever. Her blood was classified as Group AB. Because of the lack of donors of homologous group

she received blood from a donor of Group O. Preliminary cross-matching gave the expected result, i.e., the donor's serum agglutinated and hemolyzed the corpuscles of the recipient but the recipient's serum had no effect on the donor's cells. When 125 c.c. of citrated blood had been administered, the patient complained of a feeling of constriction in the chest. The transfusion was promptly discontinued but extreme dyspnea and cyanosis ensued. There was a severe chill and the oral temperature rose to 106.2° F. Two hours later the patient's serum was tinged with hemoglobin and the van den Bergh reaction was 2.0 biphasic. No hemoglobin appeared in the urine and 36 hours later the van den Bergh was 0.5 indirect. The symptoms lasted only a few hours and the puerperal infection resolved by crisis. Examination of the donor's serum demonstrated an α hemolysin active in a titer of 1:12 to 1:20 and a corresponding agglutinin active in a dilution of 1:80. The β agglutinin was titered at 1:12.

Case 9. P. S., a 16 months old girl, with athrepsia and nutritional anemia was classified as blood Group AB, and received 150 c.c. of Group AB blood after preliminary cross-matching had shown no incompatibility. Three and one-half hours later the rectal temperature rose to 104.5° F. and the pulse was 140 per minute. Hemoglobin was found in the urine. The bloods were retyped and again both classified as Group AB. The recipient's serum, however, was found to agglutinate the donor's corpuscles. The same serum was tested against the corpuscles of several bloods of Groups A and B. It agglutinated most Group B cells but not those of Group A. Two weeks later another transfusion of 150 c.c. of another Group AB blood was given. The rectal temperature rose to 102° F. but no hemoglobinuria was noted. The patient made an uneventful recovery.

Case 10. K. A., a 26 year old woman, had pyelitis of pregnancy with intermittent fever. Her blood was classified as Group B. On May 28, 1936, she received 500 c.c. of citrated blood from a Group B donor. This was followed by a chill and an oral temperature of 104° F. On June 16, 500 c.c. of blood from another B donor were given. The urine had been alkalinized prior to transfusion. Fifteen minutes later she had a chill with nausea and vomiting. The oral temperature rose to 102.4° F. The next morning she appeared deeply jaundiced. By three in the afternoon the icterus had noticeably diminished. No hemoglobin was found in the urine. Early on June 18 spontaneous labor occurred and a premature infant was delivered which soon died. The patient made an uneventful recovery. Repetition of the cross-matching showed no incompatibility.

Blood chemical studies:

Date 1936	van den Bergh	Blood Urea Nitrogen mg. %	Blood Uric Acid mg. %	Blood Creatinine mg. %
June 16	0.3 direct	Transfusion		
June 17	20.1 direct	33.6	4.2	1.6
June 18	8.2 direct	25.9	4.8	1.4
June 21	1.0 biphasic	28.0	3.1	2.0
June 26		29.4	3.8	1.2

Pulmonary Edema Following Blood Transfusion

In addition to the pulmonary edema which constitutes one of the terminal features of uremia from any cause, it has been commonly recognized that overburdening of the circulation with large volumes of fluid sometimes pro-

duces the condition directly.[21] Plummer[22] recently reported five deaths from pulmonary edema after blood transfusions in Charing Cross Hospital.

Case 11. E. S., a woman 30 years old, entered the hospital with a septicemia due to *Streptococcus hemolyticus.* She was suffering intense pain from a thrombophlebitis in a large cavernous hemangioma involving the entire right arm. The heart was normal in size and rhythm by the usual physical diagnostic criteria. There was a soft, blowing, systolic murmur at the cardiac apex. The lungs were clear. A moderate secondary anemia was present. Her blood was classified as Group A. After preliminary cross-matching on February 21, 1937, she received 500 c.c. of citrated blood from a Group A donor along with 200 c.c. of isotonic saline solution. The administration of the solutions required one hour and 10 minutes. There were no immediate symptoms but about one hour later she became extremely dyspneic and cyanotic and complained of indefinite pains in the thighs and legs. The heart appeared normal except for a rate of 130 per minute. Some coarse râles were present in the left lung. The symptoms were partially alleviated for a time by the administration of 0.5 c.c. epinephrine hydrochloride, 16 mg. (gr. ¼) morphine sulphate, and atropine sulphate 0.4 mg. (gr. 1/150) but she died eight hours after the transfusion was begun.

The donor's and recipient's bloods were re-typed and re-cross-matched after the transfusion using the hanging-drop, Vincent open slide, and the Landsteiner centrifuge methods. No incompatibility could be demonstrated.

Autopsy: The anatomic diagnoses were: *Streptococcus hemolyticus* septicemia; cavernous hemangioma of right shoulder and arm; pulmonary edema and congestion. There was no cardiac dilation.

Case 12. H. H., a woman, aged 43 years, had chronic glomerular nephritis with secondary anemia. Before admission she was said to have had hypertension but during her stay in the hospital the blood pressure was about 140 mm. of mercury systolic and 70 mm. diastolic. The heart was moderately enlarged and there was slight pitting edema of the ankles. The urine contained a moderate amount of albumin and a few leukocytes. No casts were seen. The hemoglobin measured 2.7 grams (Haden-Hauser), erythrocytes numbered 1,300,000 and leukocytes 21,200 per cu. mm. Her blood was classified as Group A. February 22, 1937, she was given a transfusion of a mixture of 450 c.c. of Group A citrated blood and 150 c.c. of isotonic saline. When 200 c.c. of the mixture had been given in 45 minutes, the administration was discontinued because of severe dyspnea and cyanosis. She was given epinephrine hydrochloride and morphine sulphate hypodermically and aminophyllin (0.48 gram) intravenously. She died one-half hour after the transfusion was discontinued. Analysis of postmortem blood gave the following values: urea nitrogen 99.4 mg. per cent and creatinine 11.8 mg. per cent.

The recipient's and donor's bloods were re-typed and re-cross-matched after the reaction occurred but no incompatibility could be demonstrated by the hanging-drop, Vincent open-slide, or the Landsteiner centrifuge methods.

Autopsy: Anatomic diagnoses—marked pulmonary congestion and edema, slight cardiac hypertrophy, chronic diffuse nephritis, anemia and hyperplasia of the bone marrow. The heart was only moderately dilated. It is very difficult to account for the production of pulmonary edema by increasing the blood volume by only 200 c.c.

Retinal Hemorrhage Following Transfusion

Ophthalmologists are acquainted with the fact that blood transfusions are occasionally followed by retinal hemorrhages.[23] The only statistical study available is that of Messinger and Eckstein[24] who examined the retinae of 60 individuals preceding and following transfusion with com-

patible blood. Ten of these patients developed retinal hemorrhages after transfusion. There was a high incidence of blood dyscrasias in the series studied, however, and the hemorrhages were most common in this group. Walker,[25] of the Department of Ophthalmology of this hospital, is at present engaged in a similar study of cases receiving transfusions. The incidence of blood dyscrasias in his series is very much lower and, so far, out of over 80 cases examined only one has developed retinal hemorrhages. The cases to be reported here are not included in his series.

Case Reports

Case 5. This has been reported above. She developed retinal hemorrhages after transfusion and during the time that there was evidence of renal insufficiency from the chronic nephritis as well as from the superimposed transfusion oliguria.

Case 3. This man had pernicious anemia and received the incompatible blood before admission to the hospital. He had extensive retinal hemorrhages but whether they followed transfusion is not known.

Case 13. A W., a woman of 69 years, had an anemia of unknown etiology. The hemoglobin was 30 per cent (Sahli), erythrocytes numbered 1,060,000 and leukocytes 4,800 per cu. mm. The leukocytes were predominately lymphocytes with an occasional myelocyte and blast cell. The blood Kahn and Wassermann tests were negative. Achlorhydria was demonstrated after histamine stimulation. The tourniquet test for petechiae, the bleeding and coagulation time, and erythrocyte fragility tests were all normal. The clot was non-retractile. The blood platelets were 0.09 per cent (Van Allen), and the hematocrit 12 per cent. Liver therapy did not stimulate reticulocytosis. There was a continuous low-grade fever. The tentative diagnosis was aleukemic leukemia, lymphatic type. Before transfusion fairly extensive hemorrhages were seen in both retinae but the maculae were not involved. The patient's blood was classified as Group A and on November 27, 1935, she received 500 c.c. of citrated Group A blood in 45 minutes, after preliminary cross-matching. Thirty minutes after transfusion there was a violent chill and the rectal temperature rose to 105° F. The next morning she complained of inability to see objects at a distance of 18 inches. Ophthalmoscopic examination revealed great extension of the preretinal hemorrhages to include both maculae. There was no hemoglobinuria or icterus and re-cross-matching of bloods by microscopic and macroscopic methods revealed no incompatibility.

She received 500 c.c. of blood from another Group A donor on December 3, with no reaction. On December 10 the bleeding time had become greatly prolonged and petechiae were elicited by the tourniquet test. On December 13 a transfusion of 400 c.c. of blood from another Group A donor had to be discontinued because of a chill and rectal temperature of 104.5° F. She died December 16, apparently of bronchopneumonia. No autopsy could be obtained. No incompatibility of bloods could be demonstrated in the laboratory after any of the transfusions.

Summary

Mortality. Seven deaths directly attributable to blood transfusions occurred in a series of approximately 3,500 transfusions. Five persons died of renal insufficiency and two of pulmonary edema (Case 3 should not be included in the statistics because the transfusion was given in another hospital). The mortality for blood transfusion in this series was, therefore, 0.2 per cent. Only one individual developing renal insufficiency in

this series recovered (Case 6) and this could not clearly be attributed to any treatment received.

Transfusion of Incompatible Blood. Many authors [1] have emphasized the importance of using typing sera of high titer. This is further illustrated by the donor in Cases 2 and 4 who gave blood as a Group O and later, with stronger sera, was found to belong to Group A. We have had five or six individuals on the donor list who were originally thought to belong to Group O but when retyped with stronger sera were found to belong to other groups, mostly to Group A.

The necessity for the cross-matching of bloods in addition to the typing is well recognized. This is further illustrated in Cases 5 and 9 where the recipients were found to belong to atypical blood groups which were not differentiated by strong typing sera and in which errors apparently occurred in the preliminary cross-matching.

Interviews with interns graduated from various medical schools and a review of their performance in managing large numbers of transfusions lead to the following conclusion: Either the importance of the laboratory technic of determining blood incompatibility is under-emphasized in undergraduate medical education or the technic itself is too difficult to be entrusted to those with the laboratory training of the average intern. Neither of these views is implied in the discussions contained in the standard textbooks on laboratory diagnosis.

It seems necessary further to emphasize the dictum that a transfusion should be discontinued immediately upon the occurrence of any unusual symptoms. This is illustrated by Cases 2 and 5 in which symptoms were ignored or considered insignificant and in Case 8 in which the transfusion was discontinued in time to prevent serious results.

Hemolytic Transfusion Reactions. We have collected considerable data regarding the van den Bergh reaction in cases of hemolysis (Cases 1, 5, 6, 8, 10). These would indicate that for the first day or so after hemolysis occurs the van den Bergh is either "direct" or "biphasic" and may attain values as high as 20.1. It promptly thereafter changes to an "indirect" reaction within the limits of normal. This conclusion coincides with the statement of Mann and Bollman.[26]

Cases 8 and 10 and the experimental demonstration of a renal threshold for hemoglobin justify the conclusion that the most reliable diagnostic criterion of a hemolytic transfusion reaction is the occurrence of hemoglobin-tinged blood serum one or two hours after the transfusion rather than the appearance of icterus or hemoglobinuria.

Both from our experience and that of other writers, we must conclude that the present laboratory tests as routinely applied involving cross-matching by the hanging-drop, the Vincent open-slide, and the Landsteiner centrifuge methods are inadequate in certain instances to detect incompatibilities of bloods which after transfusion become manifest clinically. This is especially illustrated by Case 6.

Renal Insufficiency from Blood Transfusion. The various theories to account for the mechanism of this phenomenon are discussed. If it is admitted that hemolytic reactions can occur without hemoglobinuria, the dogma that anuria occurs only after hemolysis cannot be proved or disproved by our studies or by the cases reported elsewhere in the literature. In all of our cases of renal insufficiency in which the blood serum was examined promptly, the van den Bergh reaction was compatible with the diagnosis of hemolysis.

In view of our ignorance of the mechanism of the renal damage it would seem that the only safe procedure at present is to alkalinize the urine prior to transfusion. This has been shown to prevent obstruction of the renal tubules by hemoglobin in rabbits and dogs. It must be assumed for the present that this mechanism also operates, at least occasionally, in humans.

The treatment of this type of renal insufficiency is at present unsatisfactory. Some cases recover spontaneously and others probably die regardless of any known therapeutic procedures. We have not attempted decapsulation of the kidneys but it has been reported to have failed in some cases. Apparently more efficient treatment depends on increasing our knowledge of the pathogenesis.

The Use of "Universal Donors." This procedure is fraught with danger unless the agglutinins of the donor have been previously titrated and found to be weak (Case 8).

Pulmonary Edema from Blood Transfusion. This complication of blood transfusion has been neglected in the medical literature. It is not the result of the administration of incompatible blood. On theoretical grounds, it would seem to be due to overburdening of the right side of the heart although it is difficult to ascribe this explanation in Case 12 where only 200 c.c. of fluid apparently produced death. It is possible that an amount of pulmonary edema small enough to escape detection was previously present. At autopsy the heart in Case 12 was only moderately dilated and in Case 11 no dilation could be found. Patients with cardiac damage and those with nitrogen retention from any cause apparently tolerate transfusions poorly.

Retinal Hemorrhages after Blood Transfusion. In patients having diseases which predispose to retinal hemorrhage, as in blood dyscrasias, transfusion is sometimes followed by bleeding into the macular region causing serious impairment of vision (Cases 3, 5, and 13).

Diagnosis of Transfusion Reactions by the Pathologist. The importance of careful postmortem examination has been stressed. Autopsies of patients receiving transfusions are occasionally very illuminating if the pathologist is familiar with the morbid anatomy of transfusion reactions. This is especially true in cases of renal insufficiency. Cases 3 and 7 were first diagnosed by the pathologist when the condition had not been suspected clinically.

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CHRONIC ATROPHIC ARTHRITIS *

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THERE has been sufficient interest and study of arthritis to warrant a somewhat detailed report on chronic atrophic arthritis. This terminology is synonymous with Type I, chronic infectious, chronic proliferative, chronic rheumatoid arthritis and arthritis deformans.

This study includes an admission analysis of 343 patients and a treatment and follow-up summary of 274 patients seen at this clinic. It does not include 280 patients a recent study of whom has been reported.[1, 2]

The patients in this study include only those having a definite chronic atrophic arthritis of the non-specific type. All other types were carefully excluded. The availability of data elsewhere[3, 4, 5, 6, 7, 8, 9] justifies the omission in this paper of discussion of the diagnostic criteria of atrophic arthritis.

A thorough history, physical and laboratory examinations were done on these patients on admission and at monthly intervals thereafter. The laboratory data required were complete blood counts, sedimentation rates (Westergren), agglutination titers of serum (reaction with standard strains of streptococci of the hemolytic and viridans type), complete stool and urine examinations and cultures and smears from foci of infection. In addition, roentgenological examination (fluoroscopic and films), metabolism tests, and blood chemistry determinations were done when indicated.

The findings on admission are summarized in table 1. They will be discussed under their separate headings.

TABLE I

General Summary

	Males	Females	Both sexes
Total patients seen	153 (44.6%)	190 (55.4%)	343
Total patients admitted			274 (76.96%)
Total patients diagnosis only			69 (23.04%)
Average age when seen	42.7 years	44.2 years	43.56 years
Oldest patient	89 years	78 years	89 years
Youngest patient	18 years	6 years	6 years
Average age at onset	36.59 years	37.28 years	36.93 years
Average duration of arthritis when seen	6.11 years	6.92 years	6.51 years
Patients showing deformities	91 (44.66%)	115 (55.34%)	206 (60.06%)
Patients showing no deformities	62 (45.25%)	75 (54.75%)	137 (39.94%)
Patients having focal infection			198 (57.73%)
Patients with no demonstrable focal infection			145 (42.27%)

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Incidence by Sex

Out of 343 patients 44.6 per cent (153) were males and 55.4 per cent (190) were females. These percentages do not show as great a preponderance in the female as compared to the males as the figures quoted by some investigators [10]; however, they are closely comparable to the percentage incidence reported by Weatherby.[10] All agree that atrophic arthritis is higher in the female.[11]

Age of Patients at the Onset of Arthritis and Age on Admission

The average age of male patients at the onset of the disease was 36.59 years; for females the average age at onset was 37.28 years, with an average age of 36.93 years for both sexes. The latter figure represents a mean between two extremes of age; namely, two years and 71 years. The highest incidence for both sexes was between the third and fourth decades of life. No important difference in sex in this regard was noted.

The average age of patients when first seen at this clinic was for males 42.7 years and for females 44.2 years with an average age of 43.56 for both sexes. The oldest patient seen was a male of 89 years; the youngest patient seen was a female aged 6 years.

The above summary indicates that although the highest incidence is between the third and fourth decades of life the disease may occur at any age and in either sex. Furthermore, no one age group is exempt.

Duration of Arthritis. Presence of Deformities

The chronicity of atrophic arthritis is quite evident when one notes the duration of the disease in this group of patients. The average durations of the arthritis when these patients were first seen were for males 6.11 years and for females 6.92 years, with an average duration of 6.51 years for both sexes.

Deformities were present in 60.06 per cent of these patients. The females exhibited a slightly higher incidence (55.34 per cent) than the males (44.66 per cent).

From this it is apparent that this disease is more or less progressive and that deformities are prone to occur. A study of the case histories of these patients indicates that the majority were "last resorters"—patients who had been under the care of competent men elsewhere—patients who had been to various spas and health centers—patients who had tried various patent medicines or other remedies obtainable—patients who came here with the final fond hope that the climate in some miraculous manner would alleviate their suffering, restore damaged joints to function or even "cure" their arthritis. It has been our unhappy experience to see patients who were sent or came here for climatic benefit during the active stage of the disease who did not think it necessary or were not advised that competent medical

supervision should be continued as long as the arthritis is active. It is amazing how fast these people without adequate treatment develop deformities. It finally becomes apparent to the patient that he is getting worse and he presents himself for medical care. How much easier it is to prevent than correct a deformity, but successful prevention is absolutely dependent upon early continuous treatment.

We must ever be on the alert—to have sufficient foresight to know that without adequate management flexion contractures, ankylosis and deformities will probably occur. In addition, it is highly important that these patients remain a sufficient time at one place; otherwise they will develop their deformities during their pilgrimage from doctor to doctor.

Focal Infection

An extensive and thorough search for foci of infection was made in this study. Out of this group 57.73 per cent (198 patients) were found to have definite demonstrable focal infection. This is a surprisingly high incidence in view of the chronicity of these cases and the low incidence reported by other workers.[12]

In table 2 are indicated the sites of the focal infections.

Table II

Location of Foci of Infection

Total cases 343	Cases with foci 198		57.73 per cent	
Throat or pharynx	alone	19.0%	with other foci	23.0%
Sinuses	alone	9.0%	with other foci	19.0%
Gingival tissue	alone	5.5%	with other foci	13.0%
Tonsils or remnants	alone	8.0%	with other foci	10.0%
Teeth	alone	6.5%	with other foci	10.0%
Urinary tract	alone	8.0%	with other foci	10.0%
(Lower) Respiratory tract	alone	5.5%	with other foci	5.7%
Female pelvis	alone	4.0%	with other foci	4.5%
Prostate	alone	4.0%	with other foci	4.0%
Gall-bladder	alone	1.5%	with other foci	1.5%
Colon	alone	0.0%	with other foci	1.0%
Miscellaneous	alone	0.0%	with other foci	0.0%

In 80 per cent of the cases the foci were found alone or in combination from the respiratory tract up. Of this 80 per cent localizations in the throat or pharynx were most commonly observed. Sinuses, gingival tissue, teeth and respiratory tract followed in the order of their respective incidence. In the remaining 20 per cent the urinary tract was involved in one half of the cases, followed by female pelvis, prostate, gall-bladder and colon in the order presented.

The highest incidence in this series is that of the throat and pharynx. The relatively low incidence of infection in tonsils as compared to that found

by other workers [9] is due to the fact that most of these patients had had their tonsils removed.

Inflammation of the throat is often so slight as to escape the notice of the physician and patient. Rarely does the patient complain of a sore throat. We have cultured all these throats. In a large number of instances the flora have contained a predominating or even pure culture of hemolytic streptococci. In search for other foci one must look to tonsils or tonsillar remnants, the sinuses, the gingival tissue and teeth. The examination of the teeth and gingival tissue should include not only roentgenological study but also careful direct examination and transillumination. The gingival tissue should be massaged and carefully inspected for pus pockets and faulty dental repair. Cultures should be done on all suspicious areas. Once a focus of infection has been found it is always necessary to determine by further search if it is primary or secondary.

It has been repeatedly brought to our attention in this study that (1) periodontoclasia may be the only focus present, that (2) the incidence of gingival infection is higher than that of dental abscess, and that (3) roentgenological examination of the teeth will but in a few cases definitely demonstrate periodontal infection.

Although sinusitis has been looked upon as a fairly benign factor in atrophic arthritis, the high incidence reported here may indicate otherwise. Its importance has been indicated by the studies of others.[13, 14]

In most of these foci we were able to demonstrate streptococci, usually of the hemolytic type, except in the infections of the urinary tract. Cholecystographic and non-surgical gall-bladder drainage evidence of gall-bladder infection was confirmed by direct examination and culture of tissue removed at operation.

The actual significance of these findings is not clear—there has been no direct evidence of their relationship to atrophic arthritis, particularly in long existing cases, yet we are firmly convinced that focal infection is important even in chronic cases. If one considers atrophic arthritis as due to three general factors, namely, infectious, external and constitutional, he may hope to remove the first and indirectly benefit the third. We have in several instances removed foci of infection in long standing cases with remarkable results. It has happened too frequently to be coincidental; however, we are at a loss to know whether the effect was due to removal of the infectious factor or to the constitutional improvement. Until we have direct evidence of the relationship of bacteria to this disease little can be stated with assurance, although it may be discussed at length.

Treatment

This group of patients has received a composite treatment as indicated in table 3. We wish to emphasize that no single treatment is specific in this group.

TABLE III

Treatment Summary

Patients treated.....		274
Receiving.....	Physiotherapy }	
Receiving.....	Dietotherapy }	201
Receiving.....	Heliotherapy }	
	or	
Receiving.....	Combination of above	69
	or	
Receiving.....	None of above	4
Receiving.....	Antigen, intravenously	122
Receiving.....	Vaccine	40
	or	
Receiving.....	Both	15
	Removal or treatment	
Receiving.....	Focal infection	198
	Non-operative orthopedic	
Receiving.....	Treatment	118
	Operative orthopedic	
Receiving.....	Treatment	11
Receiving.....	Blood transfusions	48

An ideal treatment plan embraces a composite program directed to the relief of pain, the amelioration of clinical manifestations, the arrest, the prevention and the correction of deformities. In table 4 an outline of treatment is given. Over a period of several years in which such a procedure has been followed we have found it most valuable.

The treatment of atrophic arthritis involves not only the active treatment but also the prophylactic treatment. We have little information in regard to the prevention of this disease, but we are convinced that the incidence of chronic cases is much too high. Unfortunately we have no means at our disposal to say which patient under certain circumstances will develop arthritis and which one will not.

Constitutional treatment is an important phase of active therapy. It involves treatment or removal of focal infections, rest, physical therapy, dietotherapy, blood transfusions, heliotherapy and climatotherapy.

Of great interest is the fact that an intercurrent jaundice may produce a remission in arthritis. For the past year and a half we have been working on the problem of "therapeutic jaundice." Recently we have evolved a technic whereby a "therapeutic jaundice" may be induced safely and with very slight reaction, either local or general. The importance of jaundice in arthritis has already been discussed by various authors in the literature. We will shortly present a paper on this subject.

REMOVAL OR TREATMENT OF FOCAL INFECTIONS

In all patients in this group in whom a definite focal infection was demonstrated this focus was treated or, when feasible, removed. Out of this group 82 per cent exhibited moderate to marked improvement on discharge, while 18 per cent of this group exhibited slight to no improvement

TABLE IV

Treatment of Atrophic Arthritis

An ideal treatment plan embraces a composite program directed to the amelioration of the manifestations of a symptomatic and constitutional disease.

I. Prophylactic.
  A. Removal or correction of:
    1. Infectious factors—early treatment or removal of focal infections before symptoms appear.
    2. External factors—avoidance of chilling, damp climates, trauma, etc.
    3. Constitutional factors—proper attention to constitutional inadequacy—conversion of the "arthritic soil" into a "non-arthritic soil" by detailed attention and treatment.

II. Active.
  A. Constitutional.
    1. Treatment or removal of focal infections.
    2. Rest.
    3. Physical therapy.
    4. Diet.
    5. Transfusions.
    6. Heliotherapy.
    7. Climatotherapy.
  B. Local—Prevention of Deformities.
    1. Rest to inflamed joints, either bed rest or by proper orthopedic appliances or both.
    2. Motion—early through painless range to prevent ankylosis, later active exercise to restore muscle tone.
  C. Correction of Existing Deformities.
    1. Non-operative.
      a. Traction.
      b. Cast wedging.
      c. Turnbuckle and other adjustable splints.
      d. Manipulation.
        1. With anesthesia.
        2. Without anesthesia.
    2. Operative.
      a. Arthroplasty.
      b. Capsuloplasty.
      c. Tendon lengthening or shortening.
      d. Osteotomy.
      e. Synovectomy.
      f. Arthrodesis, etc.
  D. Antigens and Vaccines.
  E. Drugs.
    1. Non-toxic.
      a. Salicylates.
      b. Iron.
      c. Rarely opiates (caution).
    2. Toxic or of doubtful value.
      a. Gold salts.
      b. Sulphur.
      c. Chaulmoogra oil.
      d. Arsenicals.
      e. Cinchophen and derivatives.
      f. Massive dose of vitamin products.
      g. Colchicine.
      h. Snake venom.
      i. Bee sting extracts, etc.

on discharge. Improvement was noted in a relatively larger percentage of patients treated for their focal infection than of the patients who had no focal infection.

As we have stated previously we feel that treatment or removal of focal infection is important despite some opinions to the contrary. We feel, in

addition, that in these chronic cases the time of focal removal and the method used are extremely important. In certain individuals one must proceed with the greatest caution lest he do more harm than good. We have been fortunate in this regard to have experienced no severe reactions. Finally, it is very important that one discriminates between infected and non-infected tissue before removal is attempted.

Rest

Rest, both local and general, is necessary in the treatment of this disease. Nearly all these patients complain of early fatigue. The patients were instructed as to the proper amount of rest during each 24 hours. Activity must be kept within the limits of fatigue. The amount of bed rest is variable. In cases with hot swollen weight-bearing joints the bed rest should be absolute until the inflammation has subsided. This may be a period of weeks or months. The joints are carried through a painless range of motion several times daily. These rest periods are always carried out with the joints in the position of extension and function and maintained in that position by the necessary appliances. Later, graduated activity and exercise may be permitted. There is no one treatment directed to the joints as valuable as rest. With it the inflamed joints are kept motionless and the weight bearing and movement trauma entirely eliminated. It is often surprising how well these mentally and physically fatigued patients respond to bed rest. Naturally in some cases only minimal rest is desirable.

Physical Therapy

Nearly all these patients received physical therapy. This includes heat of all types, light, massage, water, mechanical and electrical modalities and other physical agents. These valuable adjuncts to the treatment of atrophic arthritis will not be discussed as there is a wealth of available publications on this subject.[3, 15, 16, 17, 18, 19, 20, 21] Our staff includes two competent physiotherapists who work under direct medical supervision. With portable equipment it is possible to treat patients at home as well as at the Clinic.

We have noted in this group little benefit derived from hyperpyrexia (induced by any means). We reserve its use to gonorrheal arthritis where it is extremely valuable.[22, 23]

The judicious use of physical therapy is important. It requires judgment and direction of administration. When so used there appears to be no doubt as to its therapeutic effectiveness.

Dietotherapy

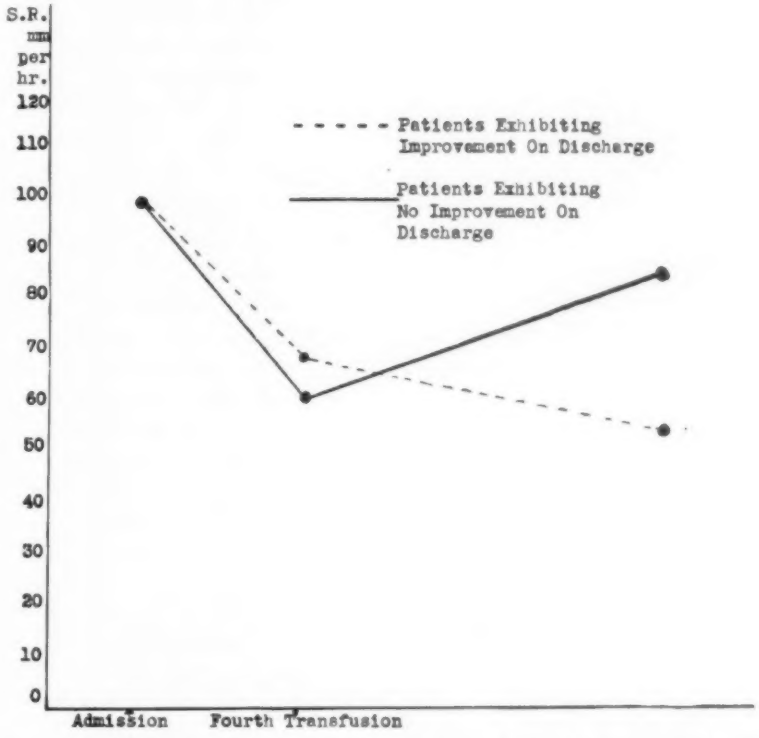
Much has been written concerning the value of diet in arthritis. Most of the patients in this study were underweight, hence they were placed upon a high vitamin, high calorie, low starch diet, supplemented when necessary (for weight gain) by milk and cream. Vitamin B was administered

routinely as wheat germ. This diet was varied occasionally to suit the needs of the individual patient. Obese patients were given the diet suggested by Pemberton.[8] It is remarkable how the doughy swelling responds to this latter diet. We have observed this same phenomenon to occur after starvation, nausea and vomiting, diarrhea and ether anesthesia. The significance of these observations has not been fully explained.

It is quite obvious that to secure constitutional improvement the underweight arthritic should gain weight, the obese arthritic should reduce. Although there are other factors concerned, dietary considerations are exceedingly important.

Blood Transfusions

Blood transfusions have been extremely useful in the treatment of certain patients of this group. A total of 198 transfusions was given to 48



Graph 1. Showing the effect of blood transfusions upon the sedimentation rate. Sedimentation rate mm. per hour (Westergren).

patients with an average of four transfusions per patient. The amount of blood given each time was from 300 to 600 c.c. or about 10 c.c. per kilo of body weight at two to six week intervals.

The effect of blood transfusions on the sedimentation rate is of interest (graph 1). It has been noted in the majority of the cases following a trans-

fusion that the sedimentation may drop to one half of its original rate. In this group this can not be accounted for solely by the improvement in the blood count. In addition, we have noted that in patients who improve the sedimentation rate following transfusions may fluctuate but the general progress is toward normal values, while in those who do not improve the sedimentation rate tends to rise toward its former level or even higher. In occasional cases the sedimentation rate may remain high even though the patient is clinically improved.

In this group receiving transfusions 66 per cent showed improvement on discharge. We do not favor blood transfusions in all cases but in certain individuals whose arthritis is particularly resistant to treatment and progressive, or who are markedly debilitated or have a persistent severe secondary anemia, transfusions are extremely valuable and should be utilized.

Heliotherapy and Climatotherapy

Nearly all arthritics of this type are benefited by a warm dry climate such as we have here in the southwest. It constitutes a valuable aid in the treatment of these patients who can spend a sufficient time in such a climate. It is equally true that a few are not benefited.

Heliotherapy was used in the treatment of the majority of these patients. Sun bathing was prescribed at a regular time, with duration and amount of exposure definitely indicated. There are a few contraindications to direct heliotherapy, namely, (1) the presence of fever, (2) the appearance of a general or local reaction and (3) complicating or debilitating conditions such as active tuberculosis, chronic myocardial disease, general debilitation and old age, etc. In febrile patients it is wise to give no direct heliotherapy but to utilize the indirect type. In case of a general or local reaction it is well to minimize the time of exposure, eliminate it entirely or to prescribe only indirect heliotherapy. We believe that both climate and sun are valuable agents in treatment.

Local Treatment and Prevention of Deformities

Rest as noted above constituted an important phase of the treatment. Graduated bed rest, splinting and rest casts should be used not only at the onset but throughout the course of the disease. An arthritic joint is always a potential deformity and should be treated as such. Properly directed physical therapy is highly beneficial. Painful joints with limitation of motion and soft tissue swelling should be moved through the painless range of motion several times daily. Exercise and activity must be within limits of pain or fatigue. It is highly pleasing to note that patients can be treated throughout the course of their disease so that when activity has subsided these joints are functionally adequate—more pleasing perhaps when one realizes that, without adequate treatment over such a period, these same patients might become permanently disabled.

Correction of Deformity

Because of the high incidence of deformities in these chronic cases their correction constitutes an important part of treatment. There are several non-operative methods available; namely, traction, cast wedging, turnbuckle and other adjustable splints and finally, manipulations with or without anesthesia. It seems very important that one proceed with utmost caution and with the dictum "do not harm." In addition, one must visualize as accurately as possible what the conditions will be a year or two years from the time of correction. It seems hardly necessary to mention that each joint should be studied extensively and other factors taken into consideration before correction is attempted. In our hands gentle, well-directed traction has been the method of choice. Occasionally we have found it necessary to resort to the other methods or even in some cases to discontinue correction because of a generalized or local reaction. Finally, it may be said that many deformities can not be completely corrected by non-operative methods and the procedure of choice should then be operative.

The operative treatment of deformity consists of synovectomy, arthroplasty, capsuloplasty, arthrotomy, osteotomy, arthrodesis, etc. It is well agreed that better results occur when the disease is quiescent. There are some indications, however, that these deformities may be corrected earlier, even during activity—in certain instances. Sufficient time has not elapsed to draw conclusion from our recent cases. It is worth emphasis that any corrective procedure should be preceded by an adequate period of preparation involving exercises, constitutional care and transfusions when indicated and followed by an equally persistent post-operative period of rehabilitation. If the disease is still active great care must be exercised to prevent recurrence of the deformity.

Antigens and Vaccines

As we have previously discussed vaccine and antigen therapy we will only mention again that we consider a patient suitable for vaccine or antigen when the sedimentation rate is high and the agglutination titers are low. Unfortunately there has been no diagnostic test of a reliable nature for determination of a patient's sensitivity to bacteria or bacterial products.

Drugs

There has been a constant parade of drugs used in the treatment of arthritis. Among them may be mentioned cinchophen and derivatives, arsenicals, gold, sulphur, chaulmoogra oil, vitamin products, snake venom, colchicine and many others. There is no proof of their specific nature and there is evidence that severe toxic reactions may result from certain drugs—notably gold and cinchophen. At this Clinic we have found acetylsalicylic acid with or without some form of calcium or sodium bicarbonate

to be valuable. There are other non-toxic analgesics of acceptable value. Opiates are to be used with extreme caution and we have rarely resorted to them. Iron is of value in the accompanying anemia. It may be best given by the oral route in fairly large doses. Subcutaneous or intravenous administration of iron appears to have no advantages over the oral route and in some cases may be dangerous. There appears to be no advantage in giving salicylates intravenously as there is sufficient evidence to indicate that their irritative properties are central rather than local.

Sulphur and gold have been disappointing in our experience but we have noted some beneficial effect with massive doses of vitamin D.[2]

Results of Treatment

It appeared worth while to correlate the time of treatment with the results. In addition, follow-up inquiries were sent to all of these patients to determine their progress since discharge. These follow-up reports came

Table V

Results and Duration of Treatment

Progress	Number of Patients	Per cent	Duration of Treatment
No improvement	35	12.82%	4.88 months
Slight improvement	28	10.68%	4.53 months
Moderate improvement	94	34.18%	7.95 months
Marked improvement	116	42.30%	8.20 months

Table VI

Results of Follow-Up Reports

	Number Reporting	Reported Condition 1–6 Years Later				
		Worse	Same	Improved	Well	Died
Patients showing slight or no improvement on discharge	21	9	8	3	1	
Patients showing moderate to marked improvement on discharge	87	9	18	30	28	2
Total	103	18	26	33	29	2

in after an elapsed interval of from one to six years and in most of the cases the elapsed time was longer than two years.

Out of this group of 273 patients 23.5 per cent or 63 patients exhibited little or no improvement during an average treatment period of 4.6 months. One to six years later follow-up reports on 21 patients of this group were as follows: nine were worse, eight remained the same, three were better

and one was well. The remaining 76.5 per cent or 210 patients exhibited moderate to marked improvement on discharge. Six per cent or 12 patients of this group were well when dismissed. The average duration of treatment was 8.1 months. Follow-up reports one to six years after discharge on 87 of these patients were as follows: 9 were worse, 18 were the same, 30 were improved, 28 well and 2 were dead.

These results indicate that of the 76 per cent of the patients treated who exhibited moderate to marked improvement on discharge, nearly all continued to improve in the years following. Some were entirely free from their arthritis and a few were worse. Out of the group (23 per cent) who showed no improvement nearly all were worse or the same, a few were better and only one was well. It is interesting to note that the average treatment time of those who exhibited moderate to marked improvement was eight months as compared to four months for those who showed little or no improvement. We feel that the length of treatment is an important factor. Patients should understand at the beginning of treatment that the course is long and will require not a few but many months of painstaking treatment. It is hoped that the time will come when we can treat this terrible disease throughout its entire course.

Summary

Admission data on 343 cases of chronic atrophic arthritis may be briefly summarized as follows: (1) Chronic atrophic arthritis runs a more or less progressive course unless treated. (2) The percentage of these patients (60.06 per cent) who showed deformities is greater than that of patients who did not. (3) All ages and both sexes were affected, the females more frequently than the males and the highest incidence was in the third and fourth decades. (4) Focal infections were found in 57.73 per cent of these patients. In 80 per cent of these cases the foci were found alone or in combination from the respiratory tract up. Foci in the throat or pharynx were those most commonly observed, followed by foci in sinuses, gingival tissue, teeth and respiratory tract in their respective order. In the remaining 20 per cent of the cases there were infections of the urinary tract in one-half; and in the remaining cases, infections of the female pelvis, prostate, gall-bladder and colon, occurring in the order of frequency given. The organism most frequently found was a streptococcus of the hemolytic type.

The treatment of this disease involves a detailed plan embracing physical therapy, heliotherapy, dietotherapy, climatotherapy, treatment or removal of focal infections, rest, both local and general, the prevention and correction of deformities, bacterial antigens and vaccines, mild analgesic and anti-anemic drugs and blood transfusions.

With such a plan 76.48 per cent of the patients treated were discharged moderately to markedly improved after an average treatment period of eight months. Of this group 6 per cent were entirely well. One to six years

later nearly all this group had maintained their improvement, or were well (33 per cent), and a few were worse. In the remaining 23.52 per cent of patients little or no improvement was noted on discharge after a treatment period of four months. Follow-up on these cases indicated that most of them were the same or worse while a few had improved. This indicates that treatment of arthritis involves many therapeutic factors which must be carried over a sufficient length of time before the maximum benefit can be derived. And, finally, that there is a certain percentage of patients who become worse or who are not benefited by treatment. It is the problems of this group particularly that should be the object of further research. Perhaps it is in this group that detailed study of the "soil" will give more information than the study of the "seed."

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TUMORS OF THE PULMONARY APICES AND ADJACENT REGIONS INVOLVING THE BRACHIAL PLEXUS *

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TUMORS which have their origin at the apices of the lung, or in the lower portion of the neck just above the clavicle, have aroused considerable interest in the past 13 years. A number of papers recently have appeared, including reports of cases that have been similar to those in the original group reported by Pancoast in 1924.

The tumors, Pancoast reported, occurred at the apices of the lungs and produced a characteristic group of clinical symptoms. Pancoast considered this type of tumor to be a distinct clinical entity and gave it the name, "superior sulcus tumor." In 1932 he reported four more cases. His criteria for diagnosis were: (1) roentgenologic evidence of a new growth at the apex of the lung; (2) homolateral pain referred along the distribution of the involved nerves of the brachial plexus; (3) atrophy of the small muscles of the hand of the side affected; (4) early development of a homolateral Horner's syndrome; (5) roentgenologic evidence of destruction of adjacent ribs and vertebrae.

Pancoast first thought these tumors to be of pleural origin but later he considered that they might be branchiogenic, arising from the fifth branchial pouch. It may be noted, at this point, that several conditions may produce the symptom-complex of pain of the homolateral shoulder and arm and cervical sympathetic paralysis; such conditions are neoplasm of the spinal cord, meninges, or cervical vertebrae, or cervical ribs or trauma. Cervical sympathetic paralysis alone may be caused by tumors of the neck, aneurysm, enlarged lymph nodes, mediastinal neoplasm, tuberculosis, and trauma.

To date, 34 cases of this unusual syndrome have been reported, 26 more or less completely. It is interesting, however, that Hare, in 1838, in addition to describing a peculiar condition of the eye, which Horner later elaborated, also gave particulars of a "glandular scirrhus in a male"; the picture closely paralleled that discussed here.

Excerpts from Hare's paper follow: "He had been attacked a month before with pain, tingling, and numbness along the course of the ulnar nerve of the left arm, which was most severe at the elbow, where there had also been some swelling and redness. There was, besides, pain through the left shoulder, extending across the chest to the opposite side, and upwards to the left eye and teeth of that side. . . . The tongue was clean, appetite good, no cough or physical sign of pulmonary disease . . . . After a

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careful examination, the only cause that could be discovered to account for his symptoms was a small tumor, situated in the 'inferior triangular space' on the left side of the neck, which it was possible might be producing some pressure on the origins of the nerves going to form the brachial plexus . . . . In addition to the foregoing symptoms the pupil of the left eye became contracted and the levator palpebrae ceased to perform its office . . . ."

Postmortem inspection revealed "a glandular scirrhus" at the base of the neck, which involved the major structures of that region, and extended downward into the superior mediastinum. The pathology and the origin of the "scirrhus" were not recorded.

This century-old report justifies the conclusion that tumors, whether primary in the cervical region, such as those arising from the fifth branchial pouch, or from the pulmonary apex, or metastatic cervical tumors, or neoplasms that infiltrate the cervical region from nearby structures will produce the characteristic group of symptoms and signs to which Pancoast called attention. A brief review of the literature shows that in Pancoast's cases 6 and 7 the symptoms may have been caused by metastasis from a carcinoma of the uterine cervix. The question of metastatic tumor may again be raised concerning the first case reported by Browder and DeVeer, while their fifth case was one of thymic carcinoma. Frost and Wolpaw reported an instance in which a sympathoblastoma arising from the inferior cervical ganglion was the etiologic agent. A squamous cell carcinoma of unknown origin was the cause of the "Pancoast syndrome," as reported by Graef and Steinberg.

General agreement now exists that the symptoms presented by a primary apical tumor are far different from those expected from a neoplasm situated at the tracheal bifurcation. Usually the symptoms of hilar tumor are cough, hemoptysis, recurrent attacks of fever and loss of weight. If there is a history of unexplained pain in the thorax or shoulder, the lungs and cervical region should be carefully examined for tumor.

To produce the Pancoast syndrome, the neoplasm must involve the brachial plexus, which has its origin in the fifth, sixth, seventh, and eighth cervical, and first thoracic segments of the spinal cord. Lesions which affect the ulnar nerve, which arises from the eighth cervical and first thoracic segments and traverses the medial cord of the brachial plexus, will implicate the small muscles of the hand. The sympathetic supply to the face and eye arises from the upper thoracic segments. Horner's syndrome, in which there is paralysis of the dilator fibers to the iris and of the superior tarsal muscle, thus causing ptosis of the eyelid, and paralysis of Mueller's retro-orbital muscle, thus causing enophthalmos, is produced in the cases under discussion by neoplastic involvement of, or pressure on, the cervical sympathetic chain, which lies anterior to the cervical vertebrae. Sweating is absent over the region of distribution of the affected nerves and a high cutaneous temperature and hyperemia are found in the same region.

Case Reports

Case 1. A white woman who presented many of the typical features of this syndrome, recently was observed at The Mayo Clinic. The patient was 64 years of age and was admitted with a history of dull, aching pain of six months' duration; the pain was in the left side of the thorax and extended to the left shoulder and arm. One year before her admission she had noted that her left eye was somewhat smaller than her right eye (figure 1). Diplopia had been present at intervals during this period. For six months she had noticed weakness, tingling and numbness of the left hand. She had lost 50 pounds (23 kg.). Cough, bloody expectoration and fever were absent.

Fig. 1. Horner's syndrome.

Physical examination revealed left enophthalmos, narrowing of the palpebral fissure and unequal pupils; the right pupil was larger than the left. The ocular fundi were normal. The head was inclined to the right and the left supraclavicular fossa was fuller than the right. Left cervical and axillary lymph nodes were enlarged and firm. The thyroid gland was normal in size but the trachea was to the right of the midline. Laryngoscopy revealed normal vocal cords. Slight pulsation was present under the left clavicle.

Pulmonary percussion revealed left apical dullness. On auscultation, bronchial breathing, but no râles, were heard in the same region. The remainder of the pulmonary fields was clear and evidence of pleural fluid was absent.

Definite enlargement of the areas of dullness over the heart and great vessel dullness also were present. A loud, systolic murmur was audible at both the apical and aortic areas; this was accompanied by a thrill over the great vessels. Blood pressure, read on the right arm, was 110 mm. of mercury systolic and 70 diastolic;

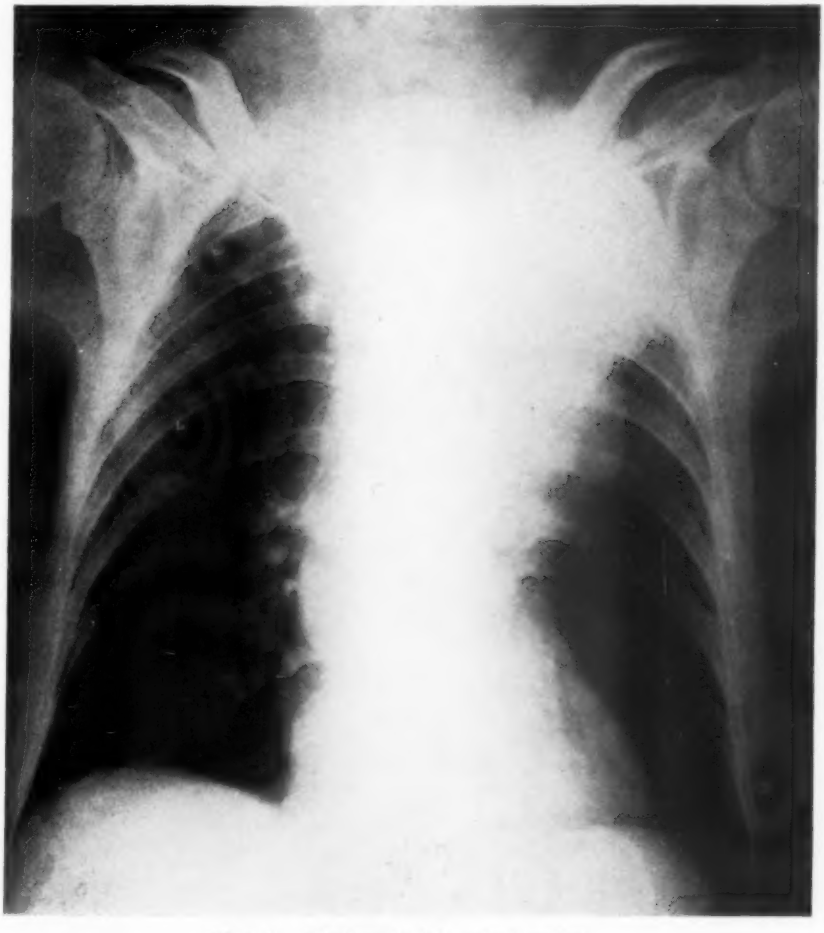

FIG. 2. Shadow in left apical region.

a reading could not be made on the left arm because of extreme hyperesthesia. The radial pulse was definitely stronger on the right.

Pelvic examination revealed a cystic mass on the right, about 8 cm. in diameter, and this was considered benign.

The left interosseous muscles, the extensor muscles of the wrist and the biceps brachii were definitely weak. Examination of the blood disclosed moderate anemia and negative Kline, Kahn, Hinton, and Wassermann tests.

There was a large, radiopaque area in the left apical region, continuous with

the shadow of the great vessels (figure 2). Apparently the ribs or vertebrae were not involved by a neoplastic process. Definite thickening of the apical portion of the parietal pleura, extending to the fourth rib posteriorly, was seen under the roentgenoscope.

Necropsy was performed one day after the death of the patient and about 10 weeks after her dismissal from the clinic. The most striking pathologic change

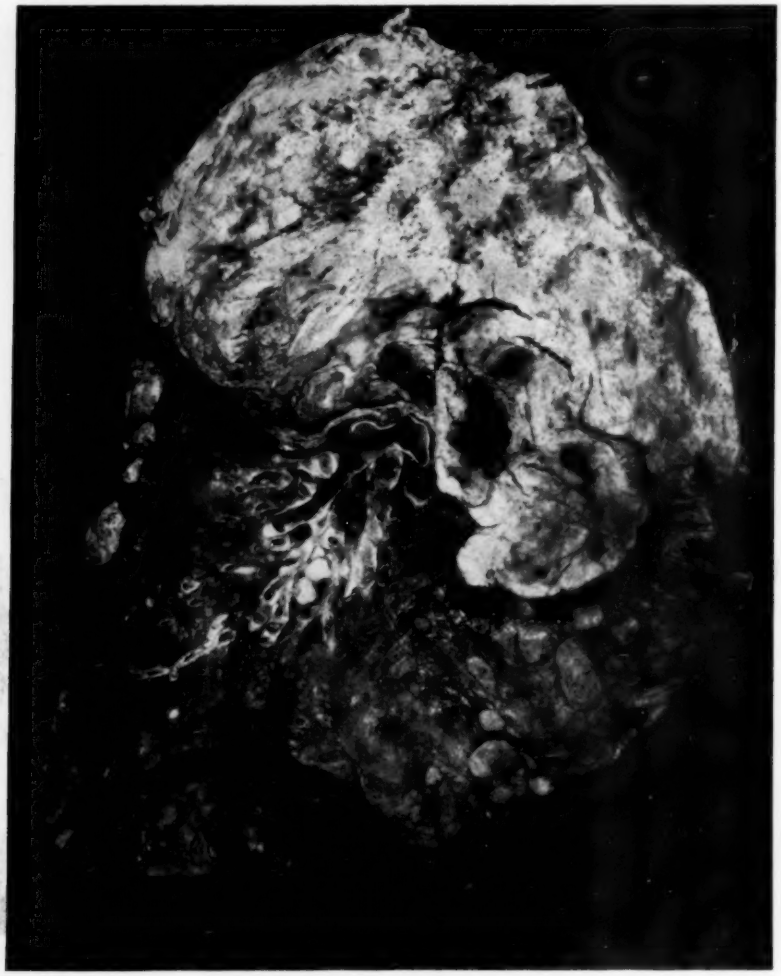

FIG. 3. Carcinoma of upper lobe of left lung and pleural implants.

was that the upper lobe of the left lung was entirely replaced by a firm, white tumor which extended anteriorly over the pericardium and about 2 cm. to the right of the median line (figure 3). The tumor also extended into the neck, lateral to the left lobe of the thyroid gland, where it invaded the left subclavian vein and brachial plexus. The bodies of the seventh cervical and first thoracic vertebrae were involved in the neoplastic process. The main tumor measured 17 by 17 by 15 cm. The cut surface was pinkish white, mottled with scattered yellowish areas of necrosis.

There was extensive metastasis to the pleurae of both lungs and to the hilar nodes. The liver also was the site of metastasis. Of further interest were calcareous changes in the aortic valve ring and a right parovarian cyst which had given rise to clinical physical signs. Terminal phenomena had consisted of severe cystitis, bronchopneumonia and left empyema. There was rather extensive chronic tuberculosis of nodes at the hilus of the lungs and there were tuberculous masses, apparently

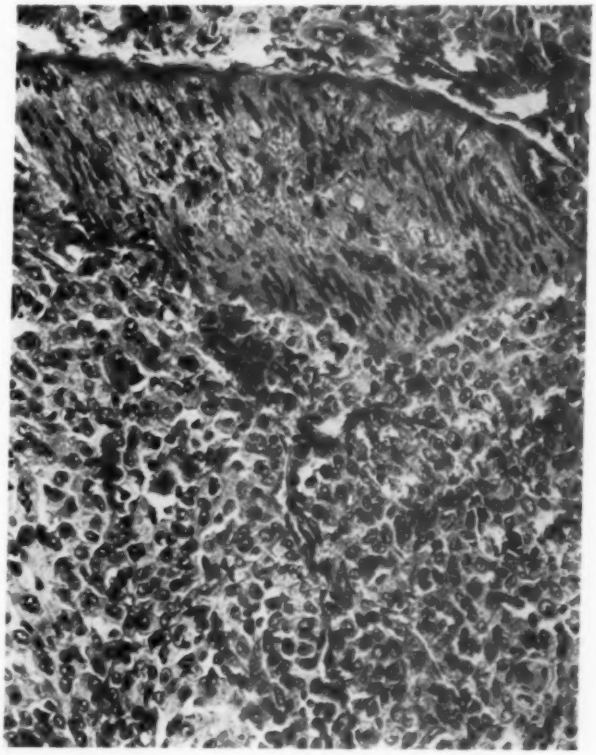

FIG. 4. Nerve of brachial plexus invaded by carcinoma.

quiescent, of the liver and spleen. Microscopically, the tumor was a squamous cell carcinoma. Figure 4 represents a section of the tumor as it involved the nerve bundles of the brachial plexus. Sympathetic nerve fibers also were involved.

Case 2. A second case which illustrates the point that any neoplastic involvement of the brachial plexus will produce the characteristic symptoms is that of a white man (figure 5), 61 years of age, who gave the following history: He had lost 60 pounds (27 kg.) and considerable strength in about 10 months preceding his admission at the clinic. He had had moderate pain in the left lower part of the thorax, but cough or hemoptysis never had been present. The left pleural cavity has been aspirated 10 times in two months; the greatest amount of fluid obtained at any one time had been 84 ounces (2520 c.c.). The fluid was the color of honey and did not contain blood that could be detected macroscopically. Guinea-pigs had been inoculated to determine if the fluid contained acid-fast microörganisms; results had been negative. Four months prior to the time of admission the man had noted a somewhat tender, firm mass in the left side of the thorax. Pain in the

left elbow had been present at irregular intervals for three months and the left arm had become weak. There had been no numbness or tingling of the left upper extremity.

The patient was somewhat emaciated. The left pupil was slightly smaller than the right and enophthalmos, grade 1, was present. A large, solid mass extended from the left axilla to the crest of the left ilium. Resonance over the left lung was diminished, tactile fremitus was absent, and breath sounds were distant. The right pulmonary field was normal. Heart sounds were of fair quality and murmurs were

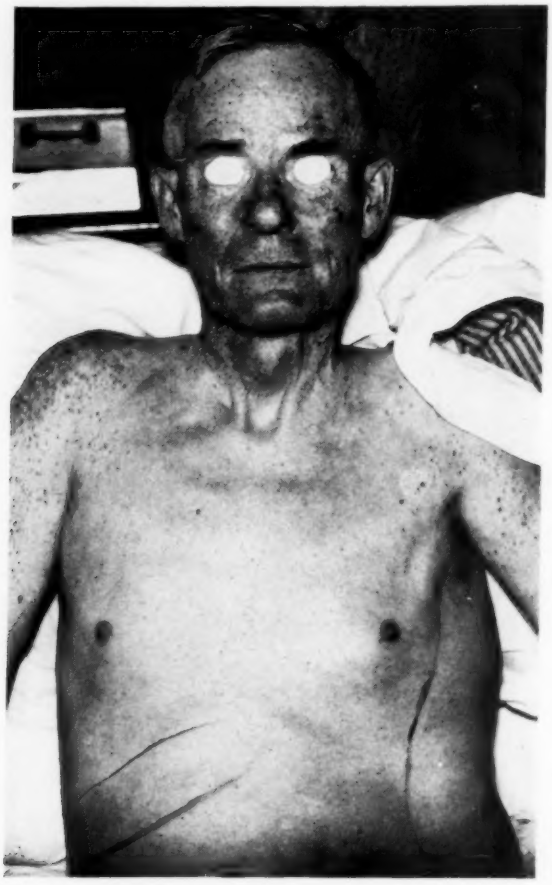

FIG. 5. Appearance of patient and extent of lesion.

not heard. The liver was enlarged so that it extended as far as the width of three fingers below the costal margin but the spleen was not palpable. The left axillary and the inguinal lymph nodes on both sides were enlarged and firm. On rectal examination, the nodes at the bifurcation of the aorta also were found to be enlarged. Moderate atrophy of the left interosseous muscles was present.

Stereoscopic roentgenograms of the thorax gave evidence of density throughout the lower two-thirds of the left lung, apparently without displacement of the heart or mediastinum. Very slight anemia was present but the sedimentation rate was

elevated to 60 mm. per hour. Examination of a stained blood smear did not disclose myeloid immaturity.

Microscopic examination of a lymph node removed from the left axilla revealed the process to be an adenocarcinoma, grade 3 (figure 6).

In table 1, the majority of the completely reported cases are summarized. Among other cases about which incomplete details are given are the following: Tobias reported four cases in which pulmonary neoplasm involved the brachial plexus. The symptoms in another case he cited were owing to a metastatic tumor, the origin of which was the stomach. Jacox cited a case of Fried, in which many of the features discussed were exhibited. Steiner and Francis reported incompletely a case of a white woman, 62 years of age, who had thoracic pain owing to a medullary type of pulmonary carcinoma with involvement of ribs. Lloyd, and Crile and Kearns made brief reference to the subject in their respective articles. Guillion and Sterne, in addition to reviewing the literature, added a case of their own. In their report they also give the details of a case of A. Ricoldoni, who published six years before Pancoast's first contribution. The report is incomplete, but an apical pulmonary tumor caused paralysis of the muscles innervated by the eighth cervical and first thoracic nerves. Pain also was

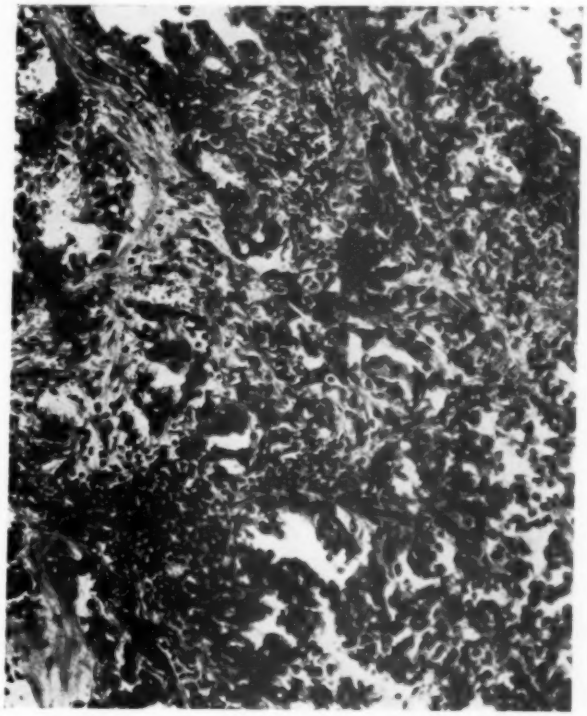

FIG. 6. Microscopic appearance of the left axillary lymph node.

TABLE I

Summary of Completely Reported Cases

Author	Age, Years	Sex	Duration of Symptoms	Chief Complaint	Wasting or Weakness of Muscles of Hand	Horner's Syndrome	Destruction of Rib	Situation of Tumor	Pathologic Characteristics	Necropsy Performed	Biopsy Performed
Pancoast	52	M.	11 months	Pain	+	+	+	Left apex	Endothelioma; diffuse scirrhous carcinoma	0	+
	36	M.	4 months	Pain	0	+	+	Left apex	Endothelioma	0	+
	60	M.	Not stated	Pain	0	+	+	Right apex	Endothelioma	0	0
Henderson	59	M.	6 months	Pain	0	0	0	Right apex	Endothelioma	0	0
	38	M.	6 months	Pain	0	0	0	Right apex	Carcinoma of lung	0	0
	35	M.	4 months	Pain	+	0	0	Left apex	New growth of lung	0	+
Pancoast	55	M.	7 months	Pain	0	+	+	Right apex	Not stated	0	0
	62	M.	8 months	Pain	0	+	+	Right apex	Not stated	0	0
	52	F.	8 months	Swollen right arm	+	+	+	Left apex	Not stated	0	0
	32	F.	2 months	Pain	+	+	+	Left apex	Not stated	0	0
Jacox	55	M.	10 months	Pain	+	+	+	Right apex	Adenocarcinoma with scirrhous elements	+	+
	44	M.	1 month	Pain	0	+	+	Left apex	Not stated	0	0

TABLE I—*Continued*

TABLE I—*Continued*

Fried [4]	45	M.	7 months	Pain	0	+	+	Left apex	Squamous cell carcinoma	+	0
Steiner and Francis	31	M.	4 months	Pain	0	+	+	Left apex	Adenocarcinoma	+	0
	42	M.	5 months	Pain	+	+	0	Right apex	Undifferentiated type of carcinoma	0	+
Clarke	53	M.	*	*	*	*	+	Left apex	Epidermal carcinoma	+	0
Fried [5]	61	M.	24 months	Pain	+	+	0	Left apex	Squamous cell carcinoma	+	0
Browder and DeVeer	57	M.	Not stated	Pain	Not stated	+	0	Left apex	Medullary carcinoma	0	+
	62	M.	9 months	Pain	+	+	+	Right apex	Squamous cell carcinoma	+	0
	62	M.	7 months	Pain	Weakness of right upper extremity	Involvement of sympathetic supply to face	+	Left apex	Squamous cell carcinoma	0	0
	46	M.	4 months	Pain	+	+	+	Right apex	Squamous cell carcinoma	+	0
	35	M.	2 months	Pain; cough	0	+	0	Right apex	Thymic carcinoma	+	0
Frost and Wolpaw	38	M.	4 months	Pain	+	+	+	Right apex	Sympathoblastoma of inferior cervical ganglion	+	0
Fried [6]	54	M.	24 months	Pain	+	+	+	Left apex	Squamous cell carcinoma	+	0
	46	M.	9 months	Pain	Not stated	+	0	Left apex	Squamous cell carcinoma	+	0
Graef and Steinberg	47	M.	6 months	Pain	+	+	+	Right apex	Alveolar carcinoma; squamous carcinoma unknown origin	+	0
Guillion and Sterne	55	M.	2 months	Pain	+	+	0	Left apex	Not stated	0	0

* Patient presented clinical and roentgenologic findings in every way typical of those described by Pancoast.

present over this area and a Horner's syndrome was found. Pulmonary signs were not present. Necropsy confirmed the clinical findings.

Summary and Conclusions

1. Two cases of Pancoast's "clinical syndrome" are presented and available published reports of cases are summarized.

2. Certain definite characteristics of these cases, owing to involvement of the brachial plexus are: (*a*) pain in the thorax or the arm, or both; (*b*) cervical sympathetic paralysis; (*c*) weakness or atrophy of the muscles of the extremity affected.

3. Absence of a history of cough, hemoptysis, and recurrent chills and fever does not militate against a diagnosis of primary pulmonary neoplasm. This point is well illustrated by the first case cited.

4. In all cases in which there is obscure pain in the shoulder and in which other parts are negative to examination, roentgenologic examination of the thorax should be made, especially if evidence of cervical sympathetic paralysis is present. Pulmonary neoplasm is not to be immediately excluded because of lack of the usual symptoms.

5. Metastasis from tumors at any point in the body, if they involve the brachial plexus, will produce the characteristic chain of symptoms noted.

6. The available reported cases of this syndrome are briefly summarized.

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CIRCULATION TIME AS A DIAGNOSTIC AID IN HYPERTHYROIDISM *

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THE satisfactory results of present day treatment of hyperthyroidism make it essential that an accurate diagnosis be made before the late effects of the disease damage the heart and other viscera. The widespread use of basal metabolism equipment indicates the acceptance of this principle by the medical profession.

It is well known, however, that increased basal metabolism is not always synonymous with hyperthyroidism. There are a number of conditions which may at one time or another in their course exhibit such elevations in metabolism. This may be noted in heart failure; in some cases of hypertension; during the course of fevers, leukemia, polycythemia, and in certain emotional states with or without evidence of disturbance of the vegetative nervous system.

The converse, hyperthyroidism with normal basal metabolism, is more rarely met with. Nevertheless, genuine instances have been reported in which the basal metabolic rate has been normal throughout the entire course of the disease.[1] Likewise, the diagnosis in an otherwise typical case may be temporarily obscured by the effects of previous iodine therapy. These considerations indicate the need for other methods of approach, in evaluating the state of thyroid function, than a study of the metabolism alone.

The work of Hurxthal[2] and others has established the fact that the cholesterol content of the blood plasma bears a somewhat approximate inverse relationship to the degree of thyroid function. While this is not altogether reliable in the individual case, it is generally agreed that in myxedema the blood cholesterol is usually elevated, while in cases of severe hyperthyroidism, it is likely to be low. The wide range of normal values for blood cholesterol renders this method less useful in the border-line case.

About 10 years ago, Blumgart began his studies on the velocity of the blood flow. After developing suitable clinical methods for determining the speed of the circulating blood, he was able to demonstrate that there is a slowing of the pulmonary blood flow in myxedema and an increased rapidity of flow in thyrotoxicosis.[3] The latter is reflected clinically in the increased pulse rate, pulse pressure, and stroke volume of the heart in hyperthyroidism. A partial explanation of the need for this increased blood flow is in the increased oxygen demands of the tissues in this disease. The red blood cells must be transported to and from the pulmonary capillaries with greater velocity in order to carry to the tissues the greater quantities of oxygen required. However, there appears to be an additional circulatory stimulant

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in hyperthyroidism which is not present in other states of increased metabolism not of thyroid origin. The latter conditions show no change in circulation time.[4]

The lack of convenient and practical methods for determining the blood velocity delayed the general adoption of this procedure into clinical medicine. However, there have appeared a number of papers dealing with the circula-

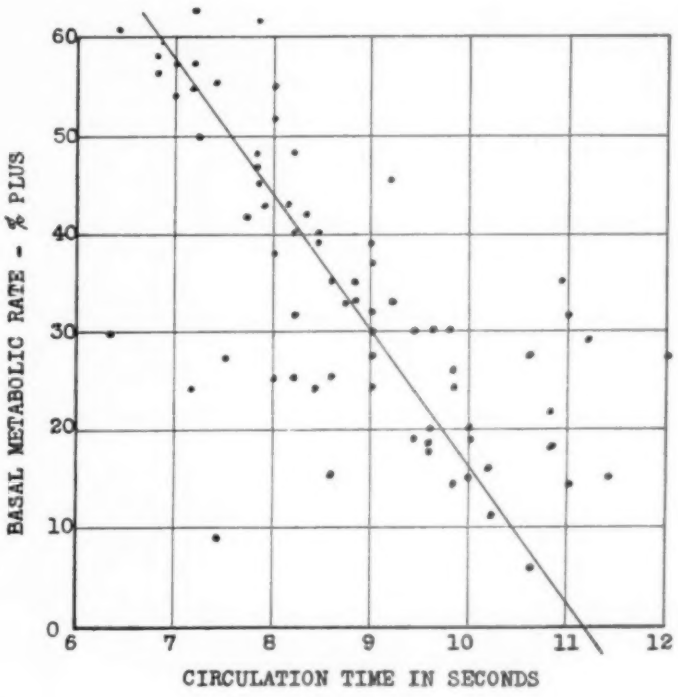

FIG. 1.

tion time in normal subjects, in patients with heart failure, and in instances of pulmonary disorders which might be confused with heart failure.[5] Blumgart,[3] Gargill [6] and Tarr, Oppenheimer and Sager [9] have studied small groups of cases of thyroid disease from the point of view of the circulation time, and have been able to show that the circulating blood flow is more rapid in hyperthyroidism. When heart failure develops in such cases, the blood flow slows up, at first manifesting what appears to be normal velocity, and when the heart failure becomes progressively more severe, the readings approach those observed in heart failure from other causes. It is probable that slowing of the blood velocity is the earliest reliable sign of heart failure and often precedes the development of symptoms.

In a previous report, I described a simple clinical method for determining circulation time, employing calcium gluconate.[7] The patient reclines, with the arm at the level of the right auricle; 2.5 c.c. of 20 per cent calcium

gluconate solution,* or 5 c.c. of 10 per cent solution, are injected into a vein at the elbow as rapidly as possible through an 18 gauge needle. The end point is that moment at which the patient first experiences an intense sensation of heat in the mouth and tongue. The term circulation time indicates the time required from the arm to the tongue (the moment of injection to

COMPARISON OF BASAL METABOLIC RATE, BLOOD CHOLESTEROL, AND CIRCULATION TIME IN PATIENTS WITH HYPERTHYROIDISM

Case No.	Sex	Age	Average B.M.R. %	Cholesterol	Circ. Time	Remarks
			plus.			
1.	F.	39	30	148 mg.	9.0 sec.	
2.	F.	47	18	170	9.6	
3.	F.	21	57		6.8	
4.	F.	45	33		9.2	Toxic adenoma
5.	M.	28	40	154	8.4	
6.	F.	39	55	138	8.0	
7.	F.	29	55		7.2	
8.	F.	40	15	200	10.0	Recurrence
9.	F.	37	18		10.8	
10.	M.	39	35	142	8.6	
11.	M.	39	46	134	9.2	Acromegaly present
12.	F.	41	63		7.2	
13.	F.	51	22		10.8	
14.	F.	18	25	180	8.0	
15.	F.	26	52		8.0	
16.	F.	40	62	95	7.8	Died before operation
17.	F.	19	48	177	8.2	
18.	F.	42	14		11.0	
19.	M.	18	27	148	10.6	
20.	F.	19	9	169	7.4	Iodine therapy
21.	M.	59	25		8.6	
22.	F.	46	35		8.8	
23.	M.	44	27		9.0	
24.	F.	40	15		11.4	Postoperative
25.	F.	23	25	160	8.2	Toxic adenoma
26.	F.	19	56	133	7.4	
27.	M.	35	42		7.7	
28.	M.	54	19		10.0	
29.	F.	39	32	134	11.0	Heart disease
30.	F.	19	30	142	6.3	
31.	F.	18	24	187	7.2	
32.	M.	40	57	129	7.0	
33.	M.	65	35	146	10.9	Rheum. heart dis.
34.	F.	—	43		7.9	
35.	M.	39	11		10.2	
36.	F.	60	24	190	9.8	
37.	F.	29	58	140	6.8	
38.	M.	42	26	150	9.8	
39.	M.	36	38		8.0	

the moment of perception). This corresponds to the path traversed by the material through the peripheral venous circuit, through the lungs, to the left heart and finally to the first peripheral arterial capillary bed off the arch of the aorta, where it is perceived as a sensation of heat in the mouth. It

* Neocalglucon, 20 per cent solution, supplied through the courtesy of the Sandoz Chemical Works, Inc.

should be measured accurately with a stop watch. The sensation descends rapidly downward, following the path of the arterial circulation. In more than 500 patients observed during the past two years, we have found this method accurate, practical and safe. There have been no accidents, no important subjective discomfort, no venous thrombosis, and no sloughs.

COMPARISON OF BASAL METABOLIC RATE, BLOOD CHOLESTEROL, AND CIRCULATION TIME IN PATIENTS WITH HYPERTHYROIDISM—*Continued*

Case No.	Sex	Age	Average B.M.R. %	Cholesterol	Circ. Time	Remarks
			plus.			
40.	M.	40	6	252 mg.	10.6 sec.	Iodine therapy
41.	F.	38	57		7.2	
42.	F.	31	47		7.8	
43.	F.	42	39	163	9.0	Rheum. heart dis.
44.	M.	33	30	170	9.4	
45.	F.	22	48		7.8	
46.	F.	45	50	140	7.2	
47.	F.	29	20	168	9.6	
48.	F.	42	33	200	8.7	Toxic adenoma
49.	F.	40	39		8.4	
50.	F.	—	43		8.1	
51.	F.	24	33	139	8.8	
52.	M.	24	40		8.2	
53.	F.	53	29	210	11.2	Toxic adenoma
54.	F.	53	37	122	9.0	
55.	M.	41	27		12.0	Liver enlarged
56.	F.	36	42		8.3	
57.	F.	34	15	130	8.6	Recurrence
58.	F.	35	45	135	7.8	
59.	F.	58	32		8.2	
60.	F.	36	30	154	9.6	
61.	F.	—	14		9.8	Iodine therapy
62.	M.	23	16	198	10.2	Mild symptoms
63.	F.	33	54		7.0	
64.	F.	18	32		9.0	
65.	F.	40	30		9.8	Early heart failure
66.	F.	36	61	250	6.4	
67.	F.	39	20		10.0	Thyroid overdosage
68.	M.	29	24	151	8.4	Thyroid overdosage
69.	F.	30	19		9.4	Toxic adenoma
70.	F.	24	18	208	9.6	Toxic adenoma
71.	F.	22	27		7.5	
72.	F.	40	24		9.0	

Average Circulation Time of 72 cases 8.8 ± 0.9 seconds

In our previous report, we established the normal arm to tongue circulation time in 60 patients to range from 10 to 16 seconds, with an average normal of 12.5 ± 1.0 seconds. These tests were not performed under basal conditions, but a short period of rest in the reclining posture was required. It was found that the pulse rate did not influence the circulation time, as cases of paroxysmal tachycardia showed normal blood velocity, but that, in common with metabolism tests, it was occasionally affected by emotional states, particularly apprehension. Under these circumstances, the reading may be verified on the following day. Normal circulation speed was found

in hypertension, bronchial asthma, nephritis with edema, and in well compensated valvular heart lesions. The circulation time was shorter in hyperthyroidism, fever and anemia and was prolonged in heart failure and in myxedema.

Including the 17 cases previously reported, we now present circulation time studies in 72 cases of hyperthyroidism. Most of these patients were being prepared for operation and the diagnosis was later proved histologically. Some were observed in the office at the time metabolism tests were being made. All patients were carefully studied clinically and by repeated metabolism tests. In many instances, cholesterol estimations were made. The average circulation time for the 72 cases was found to be 8.8 ± 0.9 seconds, the variation being from 6.3 to 12.0 seconds. The latter reading was encountered in a patient with severe muscular weakness, and an enlargement of the liver that could not be definitely attributed to heart failure. It should be remembered, however, that a relative slowing of the circulation in a patient with hyperthyroidism of long duration should always arouse a suspicion of latent or beginning heart failure. In the accompanying table, we have indicated the average of the two highest metabolism readings, as the circulation time tests were not always done on admission. In many instances, they were not performed until after the patient had begun preoperative iodine medication. Cholesterol determinations are also shown for comparison. In the accompanying graph, correlation points have been plotted indicating the circulation time and basal metabolic rate. It will be noted that the values for circulation time and basal metabolism follow a definite trend and that the distribution of the majority does not depart widely from the mean. It would appear on the basis of this evidence that a shortening of the circulation time is characteristic of hyperthyroidism, and that there is a definite relation between the rapidity of the blood flow and the height of the metabolism in this disease.

We have also demonstrated to our satisfaction, although we cannot present the evidence here, that conditions other than hyperthyroidism which give an increased rate of metabolism are associated with normal circulation time. In following some of our thyrotoxic patients after operation, a return to normal of the circulation time has been observed. In two cases, mild myxedema developed some months after operation, and the blood flow became correspondingly slowed.

Patient 20 was admitted, having received iodine medication before coming to the hospital. Basal metabolic rate on the following day was plus 9 per cent. A circulation time reading of 7.4 seconds strongly supported the original diagnosis of hyperthyroidism. Any doubt as to the correct diagnosis was dispelled by the rising metabolism after iodine had been temporarily discontinued, by the development of a postoperative thyrotoxic crisis, and subsequent histologic study of the thyroid gland.

Summary

The calcium gluconate method of determining circulation time was employed in 72 patients with hyperthyroidism. The average rate was found to be 8.8 ± 0.9 seconds, as contrasted with an average reading of 12.5 ± 1.0 seconds in 60 normal subjects. Evidence is presented to indicate that the circulation time test is useful in the diagnosis of hyperthyroidism. The test is accurate, simple to perform, and entirely safe, as indicated by an experience of more than 500 patients with various clinical conditions. It is suggested, furthermore, that a consideration of the circulation time and blood cholesterol in addition to the conventional basal metabolism test affords a more accurate and balanced interpretation of the state of thyroid function than dependence on one method alone.

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THERAPEUTIC EXPERIENCES WITH COBRA VENOM *

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Introduction

The materia medica of the ancients abounded in preparations taken from the animal world. Primitive physicians believed that the organs, secretions and excretions of all kinds of animals, including man, possessed mysterious medicinal virtues. Such animal preparations therefore figured largely in the materia medica not only of the Egyptian, Assyrian and Babylonian but also of the Greek and Latin periods and continued to flourish in the kako-pharmacy of the Dark Ages. Even after the Renaissance, at the dawn of modern medicine, the old dispensatories and pharmacopoeias listed a surprisingly large number of "preparations" derived from the animal world. To make them more impressive there were appended to these preparations such Greek, Latin and Hebrew names as appear, for instance, in the Pharmacopoeia Londinensis or New London Dispensatory of William Salmon, Professor of Physick (London, 1702). When the era of modern rational therapeutics and experimental pharmacology had begun, however, most of these preparations were dropped from materia medica but in the past two decades the medicinal use of animal products has been revived to a great extent, largely on account of the developments in the science of endocrinology and the discovery of the vitamins.

Serpents, however, have retained a place of honor in all materia medica from time immemorial. In recent years snake venoms have become the subject of both experimental laboratory and controlled clinical investigation. Their therapeutic uses fall into three distinct categories. One group of venoms, composed mostly of the *Crotalidae* or rattlesnake family, has been used empirically in epilepsy. A second group of snake venoms has been employed in connection with the treatment of blood diseases and used particularly for the control of hemorrhage. In this group are included the American moccasin, *Ancistrodon piscivorus*, the tiger snake, *Notechis scutatus*, and the tropical serpent, *Viper russellii*. But by far the most interesting group from the standpoint of pharmacology and therapeutics is the venoms of the cobras. These have received the greater amount of experimental scientific attention and their therapeutic applications are also of major importance.

It is interesting to note that in the year 1929 an American physician, the former Adolph Monaelesser of New York City, gave the first impetus to the study of cobra venom. This wealthy physician, who traveled extensively,

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became interested in the curious case of a Cuban leper who, instead of succumbing to the bite of a poisonous tropical spider, was relieved of the excruciating pains in his arm from which he had long been a sufferer. This observation suggested to Monaelesser the possibility that some animal poisons might serve as pain-relieving agents and he communicated his thoughts on this subject to Calmette, distinguished savant of the Pasteur Institute who, far from ridiculing the idea, thought it worth putting to a test. Monaelesser in collaboration with the French physicians, Oliveira and Dumatras, began an examination of snake poisons. The three physicians finally selected for their special study the venom of the cobra, probably because it is richest in those substances to which the name of "neurotoxins" has been applied. These substances, the chemical nature of which is still unknown, exert their poisonous effects on the nervous system. The results the French investigators obtained in their studies with cobra venom read like a fairy tale but cannot be recounted here in detail. Suffice it to say that the scientists of the Pasteur Institute finally reported that injections of small and safe dosages of cobra venom effectively relieved severe pain of chronic character and particularly that of advanced and hopelessly malignant tumors. In concluding these introductory remarks, the writer desires to mention the interesting fact that 800 years ago the famous Hebrew physician and philosopher, Maimonides, the prototype of the physician in Scott's novel, "The Talisman," stated in his medical treatise, *Pirque Moshch* (ed. Vilna, 1914, chap. 9, p. 26) that snake venoms were useful in the treatment of *tza-ra-ath*, or "leprosy," and *sar-ton*, or "cancer."

Cobra Venom as an Analgesic

Cobra venom was thus first scientifically employed by scientists of the Pasteur Institute, who found it useful in relieving the severe pains of malignant diseases. A number of well-known names are connected with this work and the literature on the subject has been given by the writer in another paper.[1] Stimulated by the reports, the present author began both laboratory and clinical investigation of the drug. In investigating this subject, the writer's object was fourfold: he wished (1) to study the pharmacology and toxicology of cobra venom according to the latest technical methods; (2) to prepare and assay biologically a sterile and safe solution of cobra venom for therapeutic use in human patients; (3) to ascertain in carefully controlled studies how effectively cobra venom alleviates the severe pain of patients with malignant tumors; and (4) to analyze the pharmacodynamic mechanism by which the drug produces analgesia or relief of pain, as described by previous writers.

The author performed most of his experiments with the venom of the Indian cobra, *Naia tripudians*, sent him in the form of dried scales by a colleague in India. Additional experiments were made with the venom of the African cobra, *Naia haji*, obtained from another colleague in Egypt. It

may be stated at once that the venom from both species acted in the same way. In connection with clinical studies of cobra venom it was very difficult at first to devise a method by which solutions of the drug could be absolutely sterilized from both aerobic and anaerobic organisms. Inasmuch as most snake venoms are easily destroyed by high temperatures and soon commence to deteriorate even at room temperature, special methods had to be employed in making the solution of cobra venom. Finally, however, there was developed in our laboratory a technic whereby a safe solution of the drug can be prepared.

The writer has devoted considerable study to the mechanism of the analgesia produced by cobra venom, a subject which he discussed in a previous paper and which had heretofore received little attention.[2] Some think that because that member of a human victim which has been struck by the fang of the cobra becomes numb and paralyzed, the venom produces a local anesthetic action. This is true when an enormous quantity of venom is injected at one place. Such a numbness, however, is in reality a manifestation of protoplasmic poison and not, in the strictly pharmacological sense, an evidence of the local anesthetic effect produced on the peripheral nervous structures. The writer has definitely established by his experiments that such minute quantities of cobra venom as have been employed therapeutically in very dilute concentrations, produce no demonstrable local anesthetic action either on the sensory or motor nerve endings or on the nerve fibers of the ascending or descending peripheral nervous system. On the contrary, all the writer's physiological or pharmacological data, derived from experiments performed in different ways, point to the pain areas in the cerebrum as the locus of the analgesia produced by injections of cobra venom. Evidence to support this conclusion has been adduced from (1) experiments concerning the antipyretic effect produced by cobra venom; (2) studies on the antagonism displayed by cobra venom for certain drugs producing epileptiform convulsions in animals; (3) experimental psychological study of the behavior of white rats trained in a circular maze; (4) special quantitative studies on pain threshold of guinea pigs and (5) special quantitative studies on pain threshold of human beings according to methods developed by the writer in connection with his study of opium alkaloids.[3, 4, 5]

The conclusion drawn from the various experiments was that cobra venom, like opium and its principal alkaloid, morphine, relieves pain through its action on the higher centers of the brain. The two drugs exhibited a marked difference, however, with regard to what may be styled the " fourth dimension of pharmacodynamics," namely, the time element involved in all pharmacological action.[6] It was found that while morphine relieves pain very promptly—that is, that the analgesia it produces is rapid in onset—the effect of the alkaloid wears off within a few hours. Cobra venom, on the contrary, does not induce analgesia rapidly. It is usually necessary to give an injection of the drug on each of several successive days before the analgesic action is fully developed. The analgesia effected by this drug, how-

ever, once it is induced, lasts much longer than that of morphine. In a separate paper the writer has described biochemical experiments which revealed that morphine is rapidly oxidized by fresh brain tissue *in vitro* and by the oxidative processes of the brain *in vivo*, whereas cobra venom remains unchanged in the brain tissue of animals injected therewith for a much longer time [7] and its therapeutic action is therefore of longer duration.

Clinical Experiences

The usual dosage of cobra venom recommended by the writer is five mouse units. A mouse unit is the quantity of cobra venom solution required to kill a white mouse weighing 22 grams within 18 hours after its intraperitoneal injection with the drug. Foreign investigators have employed much larger doses,[8] but the writer deems it wiser to begin with small therapeutic doses and to study each clinical case carefully before the optimum dosage for the individual patient is established. Five mouse units is a dose below the average and certainly quite innocuous. Cobra venom is not as poisonous as some well known alkaloids and even less toxic than the glucoside ouabain, which is generally regarded as but a heart stimulant.[9] Of course, there is no difference between drug and poison. Every drug may under certain conditions become a poison and, *vice versa*, almost every poison may occasionally become a useful medicinal agent. It is the writer's usual procedure to first inject but one half the contents of an ampule, or 2½ mouse units. On the following day, a whole cubic centimeter (5 mouse units) is injected. Similar doses of 5 mouse units each are injected for several successive days until a definite analgesia is noted or a contraindication for the use of the drug is encountered. In the writer's experience the latter sequel is very rare. Once analgesia has been established, patients may usually be kept comfortable with two or three injections of 5 mouse units each a week. The writer has personally administered two such injections twice a week to patients with advanced and hopelessly malignant cancers for months in succession and been able to keep them comfortable by using no other drug than cobra venom.

The injections are given intramuscularly. Local reactions have been unimportant.

In the subjoined table are classified the pathological conditions in which cobra venom has been employed by various physicians in collaboration with the writer. He is especially grateful for the coöperation of Dr. Curtis F. Burnam of the Howard A. Kelly Hospital, who was one of the first and most interested collaborators in the work, and also for the continued interest of the late Dr. Joseph Colt Bloodgood of the Johns Hopkins Hospital in this connection. The clinical studies reported here have been carried on for several years and the writer is unable to name the numerous colleagues who have so kindly reported their experiences to him.

TABLE SHOWING CLASSIFICATION OF CASES

Cancer of breast 20	Cancer of ovaries 4	Cancer of stomach 2
Cancer of uterus 35	Cancer of tongue 5	Cancer of orbit 1
Cancer of rectum 13	Cancer of floor of mouth .. 3	Myxolipoma 1
Cancer of jaw 13	Cancer of primary glands .. 5	Intestinal adhesions 1
Cancer of bladder 7	Cancer of prostate 5	Pyelocystitis 1
Cancer of retroperitoneal tissue 6	Cancer of penis 1	Raynaud's disease 1
	Cancer of spine 5	Angina pectoris 2
Cancer of lungs and mediastinum 6	Cancer of thyroid 2	Arthritis 10
	Cancer of tonsils 2	Tic douloureux 6
Tumor of bone 5	Cancer of antrum 1	Other neuralgias 10
Epithelioma 4	Cancer of larynx 1	Morphinism 3
Cancer of Fallopian tubes . 1	Cancer of intestines 3	Parkinson's disease 15

Total number of cases studied 200

Of the 185 cases enumerated in the table (15 cases will be discussed separately), 70 per cent showed definite relief of pain and in 10 per cent more of the cases some slight relief of pain was manifested. Twenty per cent of the total number either experienced no relief at all or were doubtful. One half the 70 per cent of patients that were definitely relieved showed marked improvement in their general condition and could dispense with other medication. The series of cases reported here is larger than that discussed for the first time before the National Academy of Sciences, and the therapeutic results obtained agree admirably with those described by Professor Saenz of the Pasteur Institute, who wrote the author as follows:

Monsieur et Cher Confrére: En ce qui concerne le traitement du cancer par le venin de cobra, un fait est désormais acquis: il a une réelle action anesthésiante dans 70 pour cent des cas traités. Nous ne pouvons pas dire le même chose au sujet de son action curative car malheureusement les cas studiés sont peu nombreux et ne permettent jusqu'à présent d'aucune conclusion.

It will be noted that Professor Saenz claimed that 70 per cent of his cases experienced relief or "anesthesia" and that he adds that cobra venom is but a symptomatic therapeutic agent and not a curative drug although studies on the effects of venoms on experimental tumors in lower animals are in progress in European laboratories.

Similar experiences have been described by Kirschen,[10] who summarizes his findings as follows:

Cobra venom injections were given 23 patients suffering from inoperable and incurable carcinoma of the gastrointestinal organs. There were 15 stomach cases, three lung cases, three intestinal cases and two breast carcinomata. The effect of treatment in most cases was to reduce pain and improve the general condition of the patient. Improvement in general condition and increase in strength were ascribed to control of pain. Morphine was reduced to a minimum and appetite was restored so that patients could take nourishment; in that way their wasting was checked. The analgesia, followed by no narcotic by-effect or mental depression, undoubtedly exerted a favorable psychological influence on the patients. The author states in conclusion that he would dislike to miss a single opportunity to use cobra venom in the treatment of inoperable and recurrent cancer and agrees with Körbler with regard to the therapeutic results obtained with this drug.

It would require too much space to describe in detail here all the cases which have been collected by the writer or to note the impressions concerning cobra venom treatment sent in by various physicians, but a few citations on this subject may be appropriate. The following interesting account is taken from a letter written by a colleague in the middle West who was originally very skeptical regarding the analgesic virtues of cobra venom:

Patient has been in a hospital for far-advanced cancer patients for one year—carcinoma of the cervix with recto-vaginal fistula. She has had considerable pain about the rectum which was not relieved by an alcohol intraspinal injection done several months ago. We had given her narcotics twice to the point of addiction, then took her off them. But they had soon again to be given in increasing quantities. Just before March 6, 1937, she received morphine (½ gr.) and dilaudid (1/16 gr.) every two hours; and she was quite nervous, irascible and hard to handle. For several months her appetite was poor and all her vegetables and other food had to be strained twice before she would touch them. Though she had rectal incontinence, she seemed constipated and her abdomen was tense.

Snake venom was started March 6. One half an ampule was given the first day and then one ampule a day for five days; after that the drug was given every other day until she had had six more injections. Not much effect was noticed until about five injections had been given but since then she has been a different person. The narcotics were gradually lessened so that now she receives a grain or ½ grain of codein at night and nothing else. She has had no snake venom injections for six days now. Her appetite has improved, so that now she eats anything and the nurses, and the director in charge, asked me to express to you their gratitude especially because they do not have to laboriously prepare all her food.

The subjoined lines from a resident physician of an eastern hospital indicate the efficacy of cobra venom solution in relieving pain caused by bone affections:

You will recall that some time ago you sent me 10 ampules (5 mouse units) of cobra venom with the request that I use it as an analgesic in cases of intractable pain. Thus far, I have been unable to use it on cases of coronary thrombosis, as you suggested, but have succeeded in prevailing upon our surgeon-in-chief to permit me to use it in the case of one of our graduate nurses who has an adamantinoma of the jaw with secondary staphylococcal infection, producing an osteomyelitis. In her case opiates (morphia, pantopon, dilaudid, etc.) had very little, if any, effect in alleviating the severe pain accompanying her condition, and it was because of this that Dr. —— permitted the house staff to use the cobra venom. Our results with it have been nothing less than remarkable, and I feel that you should know about them.

After a preliminary dose of 2.5 mouse units, she received 5 units daily for two days. At the end of this time she became rather stuporous, so that cobra venom was discontinued for three days. Then it was begun again in doses of 2.5 mouse units (0.5 c.c.), and she has been receiving this dosage every two days. It has relieved her pain almost entirely, and for the first time in her clinical course of almost a year here at the hospital, she has had sedation and rest. No narcotics have been given in conjunction with the cobra venom. At night she receives nembutal, from 1.5 to 3.0 grains, and this has been sufficient recently to induce sound sleep.

Again, a physician on the Pacific coast, who has used many ampules of cobra venom solution, states that the drug has proved highly satisfactory in the treatment of cancer cases suffering much pain:

In cancer patients the relief has been highly satisfactory, and the injections have not apparently been required oftener than every two to four days, an average of about three days. . . .

In severe arthritis—chronic hypertrophic and atrophic—the results have been fully as good as "one could expect." In all persons there was surcease from mental depression, which relief lasted from two to five or six days.

The following excerpt is taken from the letter of a Canadian physician who treated a confrère for advanced carcinoma of the rectum. This case was remarkable in that the patient survived for many months, kept comfortable by regular injections of cobra venom solution:

We are pleased to advise you as to the progress of the case of Dr. S——. Prior to the injection of cobra venom he was receiving as much as 4 H.M.C.'s number one with quarter grain of morphia added at times. He received the first ampule of cobra venom February 19 with no untoward effects noted. This was repeated the following day and again on the 21st. During the first few days we had to resort to narcotics only occasionally. By the third day his relief from pain was almost absolute. Since his third injection there has been complete and lasting disappearance of his previously excruciating pain. It was observed that for a few days following the third injection he lost his sense of taste; this, however, has returned.

The subjoined report concerns one of the unfortunate sequelae of radiation treatment in cases of malignant disease. This patient had a cancer of the roof of the mouth and was vigorously treated with radium, which caused complete disappearance of the malignant tumor but resulted in a persistent and extremely painful ulcer on the same surface. The patient's son, himself a physician, describes the results of cobra venom therapy as follows:

May I begin by saying that I can never thank you enough for the cobra venom you sent me for my father. I would have reported my results to you before this had not my father's condition been very poor for some time following the sudden death of my mother. However, at the present writing he is almost his old self again. He was in my office today, having driven himself in from the country, a distance of about 16 miles (incidentally, to have a plate adjusted by the dentist). His condition had so markedly improved after the first 11 injections of cobra venom that when he received in addition two more doses from the last lot you sent, all pain subsided and I saw no need to give him any more. The ulcer in the roof of his mouth has completely healed but has left an opening through the hard palate. Practically all tenderness has vanished so that he can wear a plate made to cover the opening with much comfort. There are no signs of any malignancy and I feel that he has almost completely recovered; anyway, his improvement appears to continue.

While cobra venom was chiefly advocated in cases of hopelessly advanced malignant tumors and their metastases, the writer during the past year or two has become interested in extending its use to the treatment of certain non-malignant conditions. Included among these are severe neuralgias like tic douloureux, cases of chronic arthritis which could not be relieved except by narcotics, and cases of angina pectoris with subacute, long-lasting paroxysms of pain. The number of arthritis cases treated with this drug is

still not large enough to warrant discussion although considerable relief of pain has been obtained in some instances.

Finally, the writer wishes to add a word as to a new indication for therapy with cobra venom. While he was studying a series of chronic arthritis cases and endeavoring to relieve their sufferings with various non-narcotic drugs, two patients afflicted with advanced Parkinson's disease with contractures and severe arthritic pains came under his observation through the courtesy of a colleague. It was deemed advisable to try the effect of cobra venom (in place of a host of antipyretics and codeine, to which they had become accustomed) on these two patients. To the surprise of attending physicians, cobra venom not only relieved the pain but also relaxed the rigidity of the muscles and produced a general amelioration of the patients' symptoms. This finding prompted a search for cases of Parkinson's disease, particularly those with marked pain and rigidity. Fifteen such cases have already been studied and it may be stated that the spasticity and pain of half that number have been definitely relieved. The number of cases thus treated is still too small to warrant any general conclusion but certainly stimulates further study on the subject.*

The *modus operandi* of the drug in such cases is probably a complex one: (1) The analgesic action of cobra venom certainly plays a rôle; (2) the anticonvulsant property of the drug may play a rôle; and (3) it is quite probable that certain peripheral effects of cobra venom described by Cicardo [11] may also be involved in the mechanism of the drug's action.

It is well to call attention to the fact that practically all the cases tabulated above had been treated, prior to administration of cobra venom, with all kinds of drugs including such narcotics as morphine, codeine, pantopon and dilaudid and in many cases had also been subjected to radiation with roentgen-rays and with radium. Very often cobra venom was used as a last resort when all the other therapeutic measures had failed, and it is gratifying to be able to state that in most of such cases the narcotics and other analgesic drugs were gradually reduced in dosage and finally dispensed with altogether after initiation of the cobra venom treatment.

The question of addiction arising at this point in his discussion, the writer wishes to state that up to the present time no signs of addiction, in the narcotic sense of the word, have been noted after as much as a year's treatment with cobra venom. Some physicians, however, have reported that their patients' mental attitude in general had been favorably affected by the drug. Whether this effect of cobra venom therapy is a true euphoria or merely the result of relief from pain and improvement in general condition

* Since the manuscript of this paper was sent the editor, the use of cobra venom in Parkinson's disease has been further investigated by the writer and other physicians. Such studies have confirmed the original findings concerning effectiveness of the drug in relieving symptoms of the Parkinsonian syndrome. The most important work done in this direction has been reported by Drs. Gayle and Williams in the February issue of the Southern Medical Journal, 1938.

of the patient cannot be definitely asserted. In the series he has studied only three cases of true morphine addiction have been brought to the writer's attention. One of these, a physician who suffered from neuritis, became an addict to morphine and dilaudid and came to a Baltimore hospital for treatment. Without the patient's knowledge, the dosage of the opiate was gradually decreased and cobra venom injections were substituted for such therapy. Finally the patient was taken off narcotics altogether and kept comfortable with the cobra venom injections. An out-of-town physician has reported that he has successfully treated two morphine addicts by combining injections of cobra venom with those of insulin. The drug has so far been found to produce no such symptom as morphine or other opiates or cocaine effects. In some cases it has been found to produce a general stimulation and improvement of the patients' psyche probably through relief of pain.

Summary

The venom of the deadly cobra, in sufficiently small doses and in sterile solution, has been found to be an efficient therapeutic agent for the relief of pain, particularly that of advanced malignant disease. Its use is being extended to the treatment of certain chronic non-malignant diseases accompanied by a great deal of pain. This drug, which is no more poisonous than many of the alkaloids and glucosides officially recognized by the medical profession, has been successfully used to displace analgesic drugs of the coal-tar and narcotic types. Like morphine, it depresses pain areas in the cerebrum but it differs from morphine in that its analgesia is slower in onset and longer in duration than that effected by the alkaloid. Modern pharmacology and therapeutics have thus restored the old empirical use of snake venoms described by the ancients to a place in the armamentarium of the progressive physician of today.

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GASTRIC SECRETION IN CASES OF PERNICIOUS ANEMIA *

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MANY authors believe that achlorhydria is a constant finding in cases of pernicious anemia. There are, however, a number of reported cases of pernicious anemia in which free hydrochloric acid was present in the gastric contents. Alsted was able to collect 32 such cases from the literature.

The cause of the achlorhydria in these cases is unknown. Faber was of the opinion that achlorhydria is always the result of atrophic gastritis which, according to him, is a constant finding in cases of pernicious anemia. Hurst, on the other hand, emphasized the constitutional factor in achlorhydria. The frequent familial occurrence of achlorhydria and of pernicious anemia, together with Conner's observation that achlorhydria has a distinct tendency to occur frequently among blood relatives of patients who have pernicious anemia, supports this view. It was Hurst's opinion that the absence of free hydrochloric acid predisposes to the development of inflammation of the mucous membrane.

There has been much evidence produced to prove that achlorhydria usually, if not always, precedes the onset of the anemia by a considerable time. Riley, Conner, Strandell, Levine and Ladd, Hurst, Faber and Gram, and Sturtevant have reported cases in which achlorhydria was found from one to several years prior to the onset of symptoms of pernicious anemia. In Strandell's series of 20 cases there was only one case in which free hydrochloric acid was found to be present before the development of pernicious anemia.

We have reviewed the records of 906 consecutive cases from the files of The Mayo Clinic, in which a definite diagnosis of pernicious anemia was made. Achlorhydria was found in all of the cases. This finding corresponds with the recent report of Sturgis on 600 cases of pernicious anemia. In none of our cases was there a return of free hydrochloric acid following treatment for the anemia. This finding is in contrast with that of Hurst, who has observed four cases of pernicious anemia in which the secretion of free hydrochloric acid returned following treatment of the gastritis. However, treatment for gastritis was not instituted in any of the cases we reviewed. Jones, Benedict and Hampton have demonstrated improvement in the appearance of the gastric mucous membrane during treatment of pernicious anemia.

In 36 of the cases a study of the gastric secretion was made from two to 21 years prior to the onset of symptoms of pernicious anemia. In the majority of these cases the concentration of hemoglobin was determined

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and a blood count was made at the time of the first examination. The findings are recorded in table 1. Those cases in which an analysis of the gastric contents was made in the two years before the first appearance of

TABLE I

Clinical Findings in Cases of Pernicious Anemia

Case	Age of Patient at Time of First Examination, Years	Sex	Percentage of Hemoglobin (Dare)	Corpuscles per Cubic Millimeter of Blood		Free HCl in Gastric Contents (Method of Töpfer)	Years Which Elapsed Between Original Examination and Development of Symptoms of Pernicious Anemia
				Erythrocytes	Leukocytes		
1	42	F.				0	20
2	59	F.	73	4,440,000	7,000	0	10
3	29	F.	71	4,950,000	7,800	0	21
4	54	F.	82		5,700	0	5
5	37	M.	79	4,670,000	7,300	0	11
6	42	M.	81	4,380,000	8,400	0	3
7	34	M.	78	4,980,000	7,900	0	10
8	51	F.	70	4,250,000	6,700	0	7
9	46	F.	76	4,040,000	6,300	0	9
10	57	M.	75	4,280,000	6,500	0	8
11	55	M.	70			0	3
12	68	M.	70	3,870,000	7,500	0	5
13	44	M.	85	5,120,000	6,400	0	13
14	53	F.	80	4,180,000	7,100	0	17
15	49	M.	79			0	18
16	54	M.	75			0	10
17	39	M.	74	4,030,000	7,500	0	6
18	39	F.				0	21
19	58	M.	75	4,590,000	4,500	0	5
20	65	M.	75	4,130,000	7,700	0	2
21	55	M.	71	4,270,000	5,500	0	11
22	30	M.	81	4,680,000	9,400	0	11
23	65	F.	75	4,760,000	7,000	0	11
24	44	F.	78	4,430,000	6,300	0	5
25	55	M.	80	4,780,000	6,800	0	4
26	48	F.	65	4,730,000	5,700	0	5
27	41	F.				0	16
28	54	F.	62	3,880,000	5,000	0	3
29	65	M.	80	4,010,000	6,400	0	3
30	35	F.	73	4,460,000	8,800	0	10
31	56	F.	84	4,980,000	6,200	0	12
32	46	M.	85		8,900	34	19
33	41	M.	70	4,230,000	6,700	0	12
34	37	F.	84	4,440,000	6,400	0	12
35	41	F.	70	4,470,000		16	17
36	54	M.		4,460,000		0	2

symptoms of pernicious anemia were purposely excluded. In the last column of table 1 is recorded the number of years which elapsed between the first examination of the gastric contents and the onset of symptoms of

pernicious anemia. Only cases in which a clear-cut history of the onset of pernicious anemia could be obtained are included.

From a study of these cases it appears that in 34 cases achlorhydria was present from two to 21 years before the first symptoms of pernicious anemia developed, and in two cases (cases 32 and 35) free hydrochloric acid could be demonstrated 19 and 17 years, respectively, prior to the onset of pernicious anemia.

The average age of the patients at the time of the original examination was 48 years. According to the figures of Vanzant, Alvarez, Eusterman, Dunn, and Berkson, about 18 per cent of normal individuals of a corresponding age group have achlorhydria.

It appears from these observations that achlorhydria almost always can be found a number of years prior to the development of the first symptoms of pernicious anemia, and we are in complete agreement with the statement made by Strandell, namely, that achylia in pernicious anemia is not a symptom due to the anemia but a factor of a far more deep-seated character.

It is noteworthy that in this group there are only two cases with achlorhydria (cases 26 and 28) in which microcytic hypochromic anemia was present prior to the development of pernicious anemia. In the remaining 34 cases the values for hemoglobin and the number of erythrocytes varied within the normal range at the time of the original analysis of the gastric contents.

A relationship between simple achlorhydric anemia and pernicious anemia has been suggested by the finding of achlorhydria in the two diseases. Heath, for instance, has reported a family in which some members suffered from hypochromic anemia whereas others had typical symptoms of pernicious anemia. Cases in which a transition of simple achlorhydric anemia into pernicious anemia occurred have been reported by Witts, Faber and Gram and others. Faber and Gram said that "there is such a close relationship between these two diseases that we have grounds for assuming a very intimate pathogenetic connection." It seems to us that the occasional occurrence of these two diseases can be explained on the basis of coincidence, and the fact that in the present group of cases only two such instances could be found makes us believe that the two diseases form definite clinical entities.

Summary

Achlorhydria was a constant finding in a series of 906 cases of pernicious anemia. In 36 cases analysis of the gastric contents was performed from two to 21 years prior to the onset of symptoms of pernicious anemia. In 34 of these cases achlorhydria was found. In two cases free hydrochloric acid could be demonstrated 19 and 17 years before symptoms of pernicious anemia developed. In only two cases was a hypochromic anemia found at the time of the original examination. We believe that pernicious anemia and simple achlorhydric anemia are separate clinical entities.

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URTICARIA—A NEW THERAPEUTIC APPROACH *

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Urticaria is a localized and circumscribed edema of the skin due to contraction and distorted osmotic balance in the superficial capillaries of the cutis. It has long been considered to be an allergic manifestation, but anyone who has dealt with chronic urticaria has encountered the refractive cases which in spite of all types of allergic withdrawals and desensitizations, will respond to no therapeutic measure. A number of cases are reported in the literature that have continued for many years without relief. Evaluating the allergic factor in the problem is unusually difficult, as this type of case gives the poorest response and is most inaccurate as far as skin tests are concerned; group diets, leukopenic indices, and patch tests are often of no avail. It has seemed to us that this problem of altered vessel permeability, plus a localized edema, could be approached, as in the treatment of other types of edema, from the purely chemical point of view. This, of course, has been done for many years with the use of ammonium chloride, hydrochloric acid, etc., but with the recent work on the sodium-potassium relationship in edema, it occurred to us that this might be an effective therapeutic approach. A review of the recent literature on potassium metabolism and the results obtained in a small series of patients have seemed to bear out this assumption.

The proportion of inorganic salts in blood serum is sodium 100; potassium 6.1; calcium 2.7, and magnesium 0.8. Normal serum contains from 320 to 350 mg. per cent of sodium and 18 to 22 mg. per cent of potassium. Many experiments have shown that deficiency of potassium induced in growing animals causes a definite stunting and if long continued results in death. Feng [1] reproduced Adrian's experiment and showed that the skin-muscle preparation of the frog, when scraped, loses its tactile excitability. He was able to prove that this loss was due to liberation of potassium from the cells of the skin; if the potassium was washed away the skin irritability returned. He was then able to show that application of potassium to an uninjured skin preparation had the same depressing effect on excitability. Dulière and Horton [2] have also demonstrated that potassium ions have the same depressant effect on muscle excitability. That is to say, when a skin-muscle preparation is irritated nature pours out an excessive amount of potassium to ease the local irritability, and the same effect may be produced artificially by application of potassium to an isolated segment. Nathan and Stern [3] in their studies of calcium and potassium content of serum in patients with various types of skin disease found that in the acute dermatoses the potassium fell to a subnormal level, and returned to normal as the skin lesions im-

* Read at the St. Louis meeting of The American College of Physicians, April 22, 1937.
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proved. Mathison [4] showed that intravenous injection of potassium caused a primary fall in the blood pressure with a secondary rise, and that intra-arterial injection caused a marked primary rise. McGuigan and Higgins,[5] repeating his experiment, found that potassium had the same action when injected by either route if preceded by epinephrin. Epinephrin increased the potassium in the blood serum; it caused vaso-constriction, contraction of smooth muscle, and cardiac depression. The site of action is directly on the peripheral arterial musculature, and an increase in serum potassium is necessary before the hypertensive effect is obtained. Many other investigators have shown that potassium produces a rise in blood pressure. D'Silva,[6] and also Schwartze [7] have noted that epinephrin causes an increase in the serum potassium. Camp and Higgins [8] have definitely shown that potassium has two actions on the heart: first, vagus stimulation, and second, an increase in ventricular irritability identical with that due to epinephrin. All of the potassium salts apparently cause this effect except potassium permanganate. The potassium threshold is always increased by epinephrin. Schwartze found an increase of 86 per cent in serum calcium following epinephrin. In all experiments potassium and epinephrin acted identically on the heart, intestines, bronchioles, kidneys, etc. One function of the adrenal gland is to maintain a constant potassium content of tissue, and when the epinephrin secretion stops, potassium accumulates in the tissue. Effects attributed to epinephrin are *actually* the effects produced by potassium migration which epinephrin causes. Camp and Higgins, in their explanation of the adrenalin reaction are quoted as follows: "Changes effected by adrenalin are actually produced by potassium. Adrenalin causes an increase in serum potassium. Potassium salts injected intravenously effect changes identical with those produced by adrenalin. This is true not only for the cardiovascular system but for the intestine, bladder, etc. This effect occurs after the removal of the adrenals. Potassium also produces fleeting hyperglycemia, but if potassium is present in large amounts the blood sugar is low."

Klauder and Brown,[9] in their work on the calcium-potassium ratio and the alteration of cutaneous irritability in rabbits have shown that there is a direct relationship between the degree of irritability and the amount of serum potassium. When the serum potassium was increased, the irritability of the skin was increased. *This is directly compatible with Feng's original experiment; that is, when the serum potassium is high it is because the utilizable potassium has been taken into the serum at the expense of the skin; and the skin irritability, therefore, is increased because it lacks the high potassium content in the cutaneous tissue which decreases its irritability.*

Many investigations have shown that there is a release of histamine in the skin in urticaria. Alexander,[10] and others have noted that if a given area is repeatedly stimulated eventually there will be no response to the histamine stimulation. This can be accounted for on the basis of Feng's work as follows: After repeated stimulation potassium is mobilized in the

given area and the irritability is finally suppressed by the increase in the skin potassium in this area.

Because of these basic facts it seems logical, therefore, that potassium should be a valuable drug in the treatment of edematous lesions of the skin for two reasons: first it lowers the skin irritability directly; and secondly, its pharmacological reaction is very similar to and definitely allied with epinephrin.

Results in the small series of patients that we are reporting are far from conclusive, but definitely indicate the therapeutic response. All of these patients had been tried on the various allergic regimes and orthodox treatment without success.

Case Reports

Case 1. D. J., white, male, aged 42. History of recurrent attacks of urticaria for 13 years. Physical examination and laboratory studies were negative. Skin tests were negative. Rowe diets gave no relief. Calcium lactate, nitrohydrochloric acid and ephedrin compounds were not helpful. On April 28, 1936, he was put on a high protein, low sodium, acid-ash diet with ammonium chloride, 45 gr. daily, and potassium chloride 60 gr. daily. In 24 hours the hives had cleared entirely and he has remained free ever since. He remained on a strict diet for eight weeks when citrus fruits were added. Discharged 15 weeks after institution of treatment on regular diet, entirely recovered.

Case 2. R. B., white, male, aged 57. Recurring urticaria of 10 years' duration. Skin tests were negative. Had had no relief from all types of allergic diets, acid regimes, ephedrin, etc. Had noticed on many occasions recurrent urticaria after taking milk of magnesia (this alkali apparently altering the calcium-potassium ratio). On the outlined regime he has had only an occasional hive and states that his skin has been better than for the previous 10 years.

Case 3. N. M., white, female, aged 60. Urticaria of four months' duration, no allergic history except migraine in mother's family. General physical examination and laboratory work were entirely negative. Various group diets were tried for four weeks without relief. Large doses of nitrohydrochloric acid and ammonium chloride caused little change. Skin tests showed a number of three and four plus reactions, but the removal of these offending foods made no change in the course of the urticaria. On April 7, 1936, patient was put on a low salt regime and nitrohydrochloric acid continued. Her next visit was five weeks later when she stated she was greatly improved but still having an occasional lesion. At this time she was put on a high protein, low sodium, acid-ash diet with 90 gr. of potassium chloride daily and has remained comparatively symptom-free since that time.

Case 4. R. L., white, female, aged 40. Has had hives all her life, severe for two and a half years. Has been under the care of a number of dermatologists and has taken vaccines, cleared up foci of infection and taken various types of diet without relief. Skin tests were inaccurate because of a general dermographia. This patient had a mild secondary anemia and a mild hypochlorhydria. She was put on a high protein, low sodium, acid-ash diet and the following is an excerpt from a letter written four weeks after leaving the hospital:

"I have made a decided improvement. Feeling generally better for longer than I can remember. I still have slight itching. Last night I ate soup with a tiny bit of salt. I had hives at 10 o'clock. Had some recurrence when I ran out of the potassium chloride."

Case 5. B. S., white, female, aged 18. Chronic urticaria, recurrent for two years and a loss of 25 pounds in weight. Recurrence of hives whenever she had a cold. Various types of diet gave no relief. No history of allergy in family. Physical examination and laboratory work were entirely negative. Was put directly on a high protein, low sodium, acid-ash diet with added vitamin D and 60 gr. of potassium chloride daily. Four days later she had very few hives and at the end of 15 days the hives had cleared entirely. Skin has remained clear except for an occasional dietary indiscretion. When last seen she was taking a fairly full general diet with simply a low sodium content.

Case 6. N. F., white, female (through courtesy of Dr. Francis E. Sultzman). This patient was an obese, mildly hypertensive, hypopituitary type of individual who had been on a low caloric diet for weight reduction. In November 1936, she developed a severe urticaria. After this had been present for one month she was put on a high protein, low sodium, acid-ash diet and the urticaria cleared up promptly, until at the end of 10 days she was entirely free from all signs and symptoms. There has never been any recurrence. She has remained on alternating low caloric, low sodium, acid-ash diet alternating at two week intervals with regular diet.

This series of patients was observed from a purely clinical standpoint; laboratory facilities were not available for the many chemical determinations necessary to make the study complete. However, all of the patients responded clinically in a manner that was most gratifying. The high protein, low sodium, acid-ash diet with added potassium chloride as outlined by Barker [11] for the relief of cardiovascular edema, and as recommended by Rusk and Newman [12] in the treatment of portal cirrhosis with ascites was devised to maintain a constant mild diuresis. This is accomplished by mild tubular irritation which the potassium produces and by the additional fluid loss which an acid-ash residue causes. Proteins, non-citrus fruits, and certain vegetables catabolize to such a residue. From this regime there results a shift in the mineral balance of the tissue fluids, with an increase in the potassium constituents at the expense of the sodium. We have employed this diet, which follows below, in two forms: one a well balanced menu of normal caloric value for those in average nutritional states, the other, of low caloric (1050 cals.) figures for those patients who are obese.

HIGH PROTEIN, LOW SODIUM, ACID-ASH DIET OF AVERAGE CALORIC VALUE

FRUITS:

3 servings daily, fresh or stewed, but should include either prunes, plums, cranberries, or currants once daily.

VEGETABLES:

2 large servings daily, especially beets, carrots, brussels sprouts, yellow corn, kohlrabi, lettuce, mushrooms, peas, spinach, kidney beans, parsnips.

MEAT:

2 servings daily.

EGGS:

2.

MILK:

1 glass.

CREAM:

½ glass.

BUTTER:
Salt-free, 6 squares.
CEREAL:
Oatmeal or wheatena; Farina, puffed wheat or rice occasionally.
BREAD:
Graham bread, 3 large slices or 6 small slices daily.
RICE, MACARONI OR SPAGHETTI:
1 serving daily.
POTATO:
1 serving.
JELLY, PRESERVES OR HONEY:
2 level tablespoons.
SUGAR:
Ad libitum—at least 1 tablespoonful.

NOTES

All foods are to be prepared without salt and no salt is to be served with meals. Potassium chloride (from 2 to 5 gm. in shaker) may be given as salt substitute. Spices—cinnamon, sage, paprika, pepper, cloves, nutmeg, allspice may be used. Small servings of citrus fruits may be added after fluid volume is established. Additional vitamin D to be supplied.

Coffee or tea, 1 cup daily.

HIGH PROTEIN, LOW SODIUM, ACID-ASH DIET OF LOW CALORIC VALUE
(APPROXIMATELY 1050 CALORIES)

BREAKFAST
1 serving of 10 per cent fruit
2 eggs
1 slice whole wheat bread 3½ by 2⅝ by ½"
Coffee with saccharin and 2 tablespoons skimmed milk if desired.

LUNCH
Veal cutlet one piece 6" by 4" by ½", or
2 veal chops, or
Lean round steak one piece 4" by 3" by ¾", or
⅔ cup ground lean beef, or
⅔ cup sweetbreads, or
Calf liver 4½ slices 2" by 3" by ¼", or
3 pair frog legs—large, or
1½ pieces fish 4" by 3" by ½"
Broil these meats with mineral oil.

Vegetables
1 serving of 5 per cent vegetables.

Salads
1. Hard cooked egg (1).
2. Cottage Cheese—¼ cup.
3. Vegetable salad of 5 per cent vegetables. If this salad is selected, add ¾ cup broth to this meal.
   Serve salad on 3 lettuce leaves with mineral oil dressing.
   Make this dressing by using your favorite French or mayonnaise recipe, substituting mineral oil for salad or olive oil, and potassium chloride for table salt.

1 serving of 10 per cent fruit.
¾ cup skimmed milk or skimmed buttermilk.

DINNER

¾ cup broth or jellied broth.
Roast veal, lean beef, chicken, turkey, or lamb 2½ slices 4″ by 4″ by ⅛″.
1 serving of 5 per cent vegetables.
Vegetable salad of 5 per cent vegetables with 3 lettuce leaves and mineral oil dressing.
1 serving of 10 per cent fruit.
¾ cup skimmed milk or skimmed buttermilk.

DIET INSTRUCTIONS

1. Eat nothing that is not on diet list.
2. Do not use citrus fruit oftener than once daily, best to omit entirely.
3. Do not use fats in cooking. Mineral oil may be used.
4. Do not use table salt in cooking or on food.
5. Do not take any alkaline medicine, as sodium bicarbonate.
6. Limit fluid to 7 cups, ¾ full, daily, including liquids consumed with meals.

The problem of potassium toxicity to which older investigators attach much importance has not been a complication in this series. Only in one patient, an anemic, emaciated individual have we noted muscular pains, vertigo, headache, sweating, and other symptoms of potassium intoxication. These were quickly relieved by a reduction in dosage. Potassium chloride in doses of 60 to 90 grains a day has been a safe drug in our hands, more readily tolerated if enteric coated.

COMMENT

The potassium-sodium-adrenal relationship is already a definitely established clinical entity in Addison's disease.[13] A sound physiologic and pharmacologic basis seems to exist for the treatment of the various allergic phenomena by further change in the already abnormally altered mineral balance. It has been definitely shown from numerous sources that in skin irritability and skin inflammation the potassium metabolism is markedly altered, and that an increase in skin potassium causes an appreciable decrease in localized irritability. It also has been shown, definitely and conclusively, that potassium is almost identically adrenal-like in its pharmacological action. Because of these known facts it seems logical that certain allergic problems could be approached from this therapeutic angle with benefit. In a small series of cases of chronic urticaria, a high protein, low sodium, acid-ash diet, with added potassium chloride, has produced promising clinical results. We hope that this small series of cases will stimulate a further trial of what we believe to be a sound and fundamental therapeutic principle.

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UPPER LOBE PNEUMONIA IN THE ADULT *

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Pneumonia of the upper lobes is neither a new nor a rare occurrence. It was described by Laennec and also by his contemporaries, Andral and Broussais. However, despite the common knowledge of its existence there have been exceedingly few references to this subject in the literature. This is equally true of the standard textbooks which deal very extensively with the general subject of pneumonia. It is not difficult to fathom the cause of this apparent neglect. The diagnosis of apical pneumonia by physical signs, alone, is attended with great difficulty and, in the absence of routine roentgenograms, the number of cases diagnosed correctly is very small and has offered little opportunity for clinical study. We have therefore made a detailed analysis of a series of cases of upper lobe pneumonia at the City Hospital with particular emphasis on the differential diagnosis, the course of the illness, and the prognosis. We hope that by calling attention to this type of pneumonic involvement the diagnosis will suggest itself in many obscure pneumonias observed in private practice without physical signs of consolidation.

As was stated above upper lobe pneumonia is by no means a rare occurrence; it is only the diagnosis which is infrequent. In a series of 522 cases of pneumonia Adams [1] found 97 instances (18.5 per cent) of isolated upper lobe involvement. MacCordick,[2] in a similar series, reported a 26 per cent incidence and Warr and Alperin [3] found a 10 per cent incidence. Our study covered a period of 21 months from August 1934 to April 1936. The total number of pneumonia cases admitted to the Second Medical Service was 180 of which 24 (13.3 per cent) had primary upper lobe involvement. There were 20 white patients and 4 colored ones and the sex incidence was 18 males and 6 females. The age groups ranged from the second to the ninth decade but the majority of the cases (70 per cent) were in the third, fourth, and fifth decades.

Three types of onset were noted, namely, acute, catarrhal, and meningitic. The first two groups included the vast majority of patients and consisted of 22 cases. There were but two instances of frank meningitic onset. Of the nine cases whose illness began acutely with chill, fever, and chest pain there were two which subsequently showed meningitic features. The catarrhal group consisted of 13 patients. All began with upper respiratory disease. Four developed pneumonia insidiously, seven had acute symptoms following the catarrhal phase, and two showed meningitic manifestations after the catarrhal period.

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From the Second Medical Service of the City Hospital, New York.

The course of the illness in these 24 upper lobe pneumonia patients was carefully analyzed. The degree of toxicity was arbitrarily divided into three grades according to the composite clinical appearance of the patients and it was found that sixteen (66 per cent) of the cases were in Grade III (markedly toxic), four (17 per cent) were in Grade II (moderately toxic), and four (17 per cent) were in Grade I (slightly toxic). The number of patients who required oxygen therapy is also an indication of toxicity inasmuch as the routine requisites for oxygen administration were a heart rate above 135, respirations above 35, or the presence of cyanosis. Eleven patients were given oxygen. The extent and type of pyrexia were also noted. There were 20 patients with temperature above 102° F. Of these 11 were continuously high, seven were remittent, and two were intermittent. There were four patients with temperatures below 102° F.; two were continuous and two were remittent.

Study of the lobe involvement of these cases according to roentgen-ray findings revealed 14 instances of single upper lobe pneumonia and 10 instances in combination with either the contra-lateral upper lobe or one of the lower lobes. The number of times each individual lobe was affected was as follows:

Lobe	Number of Instances Involved
Right upper	19
Right middle	1
Right lower	4
Left upper	7
Left lower	6
Right and left upper combined	2

It is of interest that in three of the cases of single upper lobe involvement no physical signs could be detected despite the roentgen demonstration of the lesions. In the cases with multiple lobe involvement the diagnosis of associated lower lobe disease by physical signs checked very closely with the roentgen-ray. The course of illness in the two groups was strikingly different. The 14 cases with single lobe involvement had a mortality rate of 21 per cent whereas the 10 cases with multiple involvement had a mortality rate of 70 per cent.

The duration of illness in the entire group of upper lobe pneumonias varied considerably. Of the 14 cases which survived five recovered by crisis and nine by lysis. The chart below depicts the number of days of illness of each of the patients and the mode of termination of the disease.

The number of cases in our series is not large enough to warrant any generalized conclusions but the above chart definitely shows that most of the patients who died did so within a 10 day period of illness. It also indicates that most of the patients who recovered by lysis were ill for a period greater than 10 days. These facts suggest that in view of the high mor-

DURATION OF ILLNESS AND MODE OF TERMINATION

	Number of Patients	Individual Duration of Illness (in days)	Average Duration of Illness (in days)
Terminated in Crisis.....	5	6, 6, 6, 9, 9	7.2
Terminated in Lysis.....	9	4, 7, 11, 16, 16, 16, 18, 22, 24	14.9
Terminated in Death....	10	4, 4, 5, 5, 7, 9, 9, 10, 11, 22	8.6

tality rate (42 per cent) in this disease a 10 day period of survival may be of some prognostic significance. In considering the condition of the pneumonic lesion in the patients who recovered there was found no instance of unresolved pneumonia in the entire group. The roentgenograms of nine showed complete disappearance of the lesion and the remaining six showed residua such as thickening of the apical and interlobar pleurae or linear fibrosis. There is a strong possibility that if these six cases had been roentgen-rayed again they also would have shown complete absorption of the infiltration. This contention is somewhat strengthened by the fact that most of them had no roentgenograms within a week of discharge. None of the patients who recovered had any physical signs at the time they left the hospital.

Most of the cases were worked up completely from the laboratory standpoint and particular emphasis was given to examination of the sputum for tubercle bacilli. There was no instance in which tubercle bacilli were found. In 20 of the cases the sputum was typed for pneumococci by the Neufeld method. The results were as follows:

Number of cases negative Types I–XXXII 13
Number of cases positive Type I 3
Number of cases positive Type II 2
Number of cases positive Type III 1
Number of cases positive Type XIV 1

There may be some significance in the high percentage of negative typings as this is in marked contrast to the results usually obtained in typing lower lobe pneumonias.

Examination of the urine in 20 cases showed nine instances of albuminuria, three instances of hematuria, two instances of glycosuria (non-diabetic), and one instance of choluria. Seventeen cases had chemical examinations of the blood. Two showed azotemia; two showed hyperglycemia (non-diabetic); and three showed cholemia. Twenty-two patients had blood Wassermanns of which two were positive. One of these recovered with complete resolution. Blood counts were done routinely on admission and when indicated during the course of illness. The figures showed nothing of particular significance. The range of leukocytosis was from 10,000 to 35,000 and the percentage of polymorphonuclear cells varied

from 45 to 95. All cases showed a decided shift to the left by the Schilling count.

No pulmonary complications were observed. However, there were many extra-pulmonary complications which were indicative of the severity of the disease. Five patients showed toxic psychoses; nine had toxic albuminuria; three had focal glomerular nephritis of whom two showed azotemia; three had toxic hepatitis. The severity of apical pneumonia particularly in regard to prostration and cerebral symptoms has been pointed out by Norris and Landis.[4]

The treatment of these cases was chiefly supportive with great emphasis on fluid intake. Oxygen was administered when necessary. One case was given serum. The inability to obtain a specific typing of the sputum in the majority of the cases was responsible for the lack of a more general use of serum therapy.

In discussing the differential diagnosis of apical pneumonia it is of considerable interest that ten (42 per cent) of the cases were diagnosed as pulmonary tuberculosis on admission. The physical signs of many of the cases, particularly those with beginning resolution, were identical with those found in tuberculous lesions. The history of acute onset with chest pain, chill, and fever, when present, was of some diagnostic value but considerable significance was attached to the presence of labial herpes which is rarely, if ever, seen with pulmonary tuberculosis. The roentgen-ray was the most valuable diagnostic aid. While lobar consolidations may occur in tuberculosis they do not undergo complete resolution within a period of two weeks as do those in pneumonia. Putrid lung abscess may resemble apical pneumonia at the onset both clinically and radiographically but the diagnosis is usually established with the expectoration of foul sputum. Meningitis must also be included in the differential diagnosis. Six of our patients showed meningitic symptoms and in two of them spinal punctures were performed because of frank meningitic signs. In these latter two instances there were neither pulmonary symptoms nor signs on admission. In a report of six cases of apical pneumonia Lepage [5] noted that three of his patients had no cough or expectoration at the onset.

Five of our patients were admitted with the diagnosis of pneumonia based on symptoms alone. No physical signs could be elicited over the affected areas despite their demonstration by roentgen-ray. Two of these cases showed physical signs during the resolution phase but the other three showed no signs on daily examinations throughout the entire period of illness. In these latter instances the diagnosis was made possible only by the roentgenograms. These facts strongly suggest the possibility that the numerous cases observed in private practice in which the patients have the typical history and symptoms of pneumonia but no physical signs are instances of upper lobe involvement.

The clinical syndrome of apical pneumonia with rapid and complete resolution of the lesion is depicted in the following case reports.

Case Reports

Case 1. M. H., a 16 year old girl, was admitted on March 12, 1936, with a history of productive cough, evening rise in temperature, and night sweats of two weeks' duration. On physical examination the patient did not appear acutely ill. There

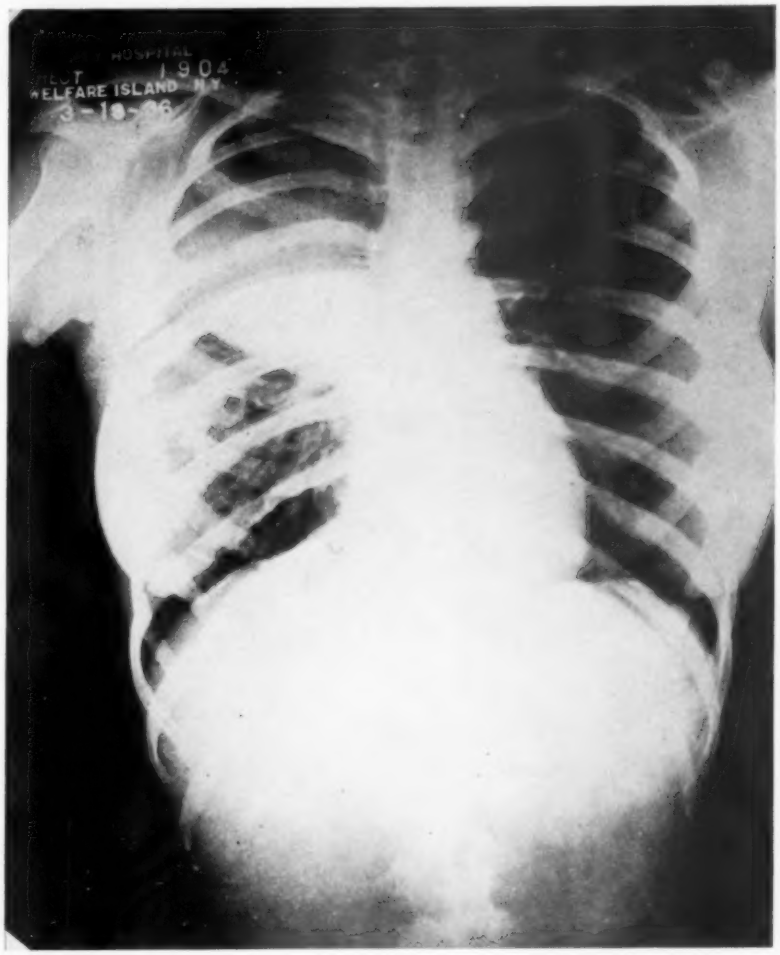

Fig. 1. (3-13-36) *Case 1.* Pneumonic consolidation of right upper lobe; small infiltration in right middle lobe. Left side negative.

were dullness and diminished breathing over both upper lobes. The temperature ranged between 99° and 102° F. The sputum was negative for tubercle bacilli and for pneumococci types I–XXXII. The admission diagnosis was bilateral upper lobe pulmonary tuberculosis. Pneumonia was considered only as a possibility. Roentgen-ray examination on March 13 showed a pneumonic consolidation of the right upper lobe and a small infiltration in the right middle lobe. The left lung was negative (figure 1.). The clinical course was uneventful and the temperature subsided gradually. Daily physical examinations revealed no signs of resolution at any time but

a roentgenogram on March 24 showed complete clearing of the lesion except for a few fibrotic strands extending from the hilum and a thickening of the interlobar pleura (figure 2).

Case 2. L. M., a 32 year old woman, was admitted on February 17, 1936, with a history of fever and pain in the right chest of four days' duration. She had noticed progressive loss of weight and weakness for several weeks prior to the onset of the

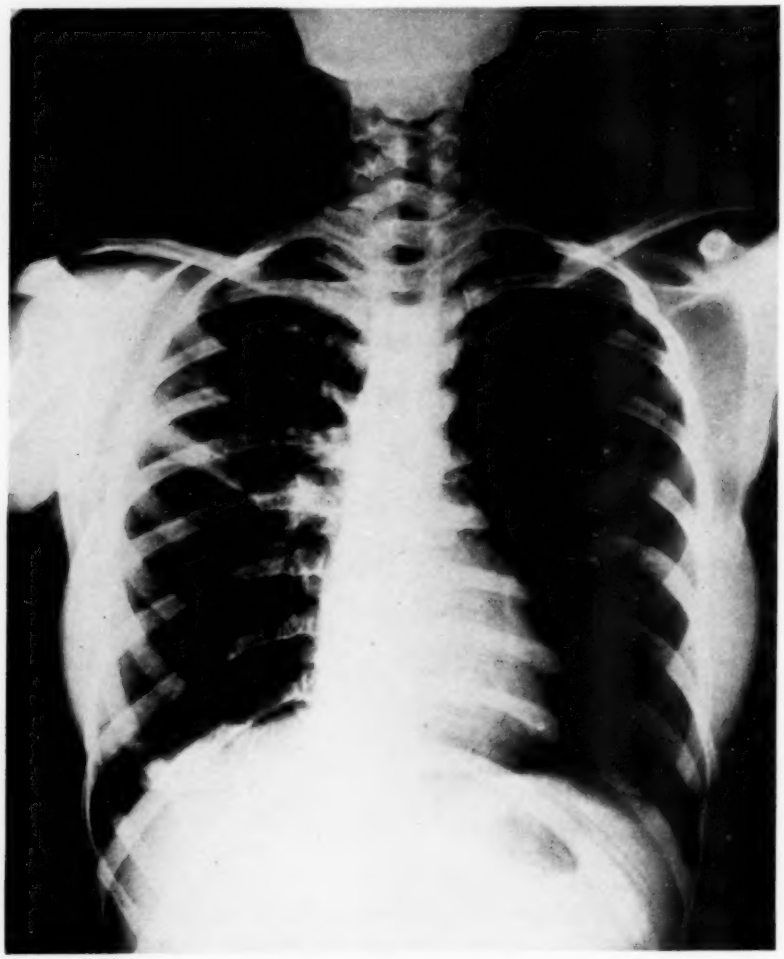

FIG. 2. (3-24-36) *Case 1.* Absorption of lesion; residual interlobar pleurisy and hilar fibrosis.

present symptoms. Examination on admission revealed the patient to be acutely ill with temperature 104° F. Herpes was present on the upper lip and there were signs of consolidation of the right upper lobe. Roentgen-ray (figure 3) confirmed this. The sputum showed pneumococci type III and was negative for tubercle bacilli. The clinical course was characterized by marked toxicity, high pyrexia, and toxic hepatitis. One week after admission the temperature began to decline and gradual improvement of all symptoms was noted. A roentgenogram on March 3 showed complete resolu-

tion of the pneumonia except for a few hilar strands and thickening of the interlobar pleura (figure 4).

Case 3. J. L., a 25 year old man, was admitted on December 1, 1934 with a history of chills and fever of two days' duration. His temperature was 104° F. Herpes labialis was present. The general appearance was that of marked toxicity but the most prominent features were nuchal rigidity, hyperirritability, and delirium

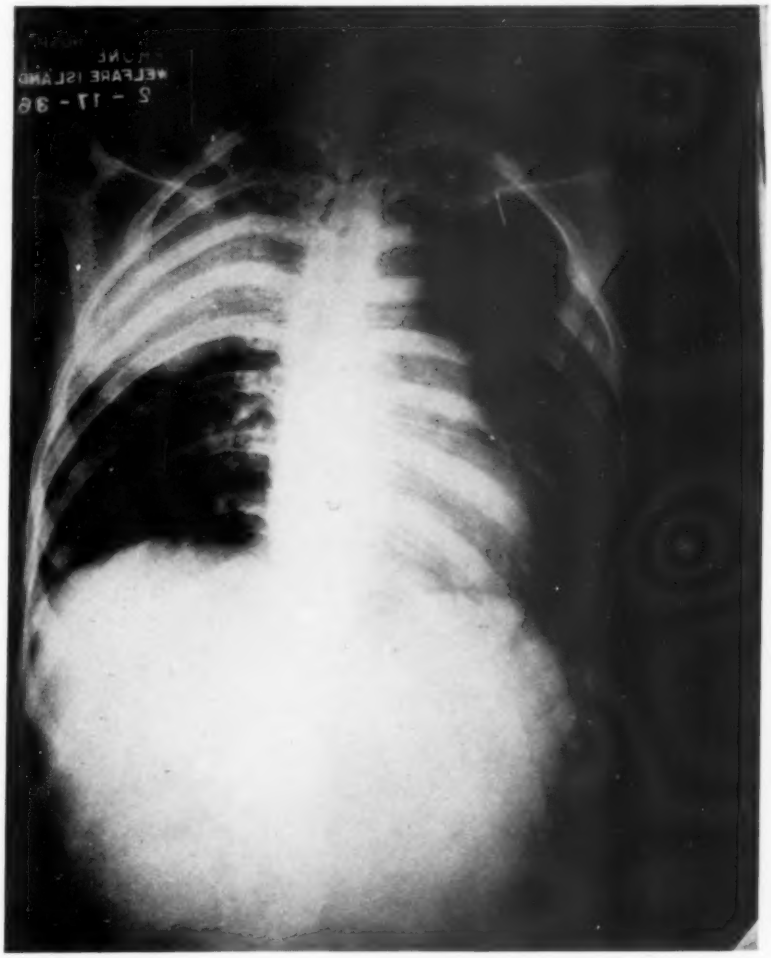

FIG. 3. (2-17-36) *Case 2.* Pneumonic consolidation of right upper lobe; remainder of lungs negative.

which were present to such a degree as to suggest the diagnosis of meningitis. Spinal puncture was done and examination of the fluid proved negative. Physical examination on admission was inconclusive but a roentgenogram on December 3 showed complete consolidation of the left upper lobe (figure 5). Pneumococcus typing of the sputum was unsuccessful; there were no tubercle bacilli present. The patient was acutely ill for nine days and then recovered by crisis. Roentgen-ray

on December 18 showed resolution of the lesion and a residual thickening of the interlobar pleura in association with a few hilar strands (figure 6).

In the studies of Sante [6] and Hart [7] on the postpneumonic lung it was found that pulmonary fibrosis and interlobar pleurisy were among the most frequent complications of lobar pneumonia. These residual effects were

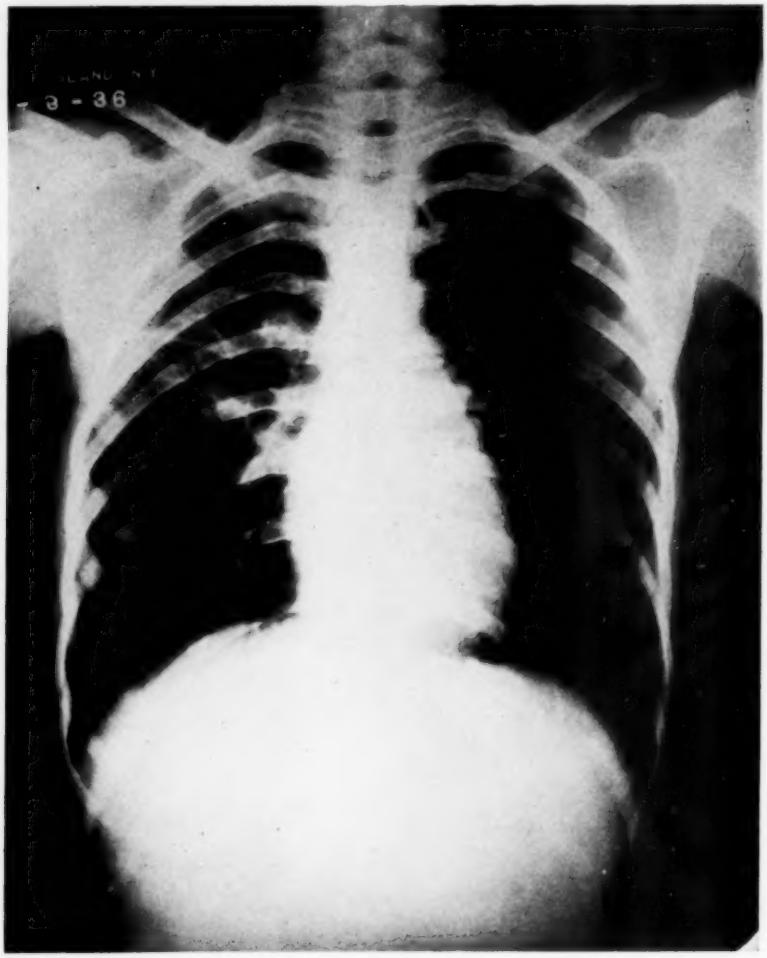

FIG. 4. (3–3–36) *Case 2.* Absorption of lesion; residual interlobar pleurisy and hilar fibrosis.

noted in many of our cases. However, there were no follow-up roentgenologic examinations after hospitalization, and it is therefore impossible to state whether or not these shadows subsequently cleared up. In cases of apical pneumonia residual fibrotic lesions are of considerably greater significance than in lower lobe disease because it is more or less customary to in-

terpret all fibrotic infiltrations in the upper lobes as tuberculous without inquiring too carefully into the history of previous pulmonary infection. The clinical and radiologic course of illness in our patients unquestionably established the diagnosis as pneumonia rather than tuberculosis and yet the residual fibrotic infiltrations in no way differed from those seen after resolu-

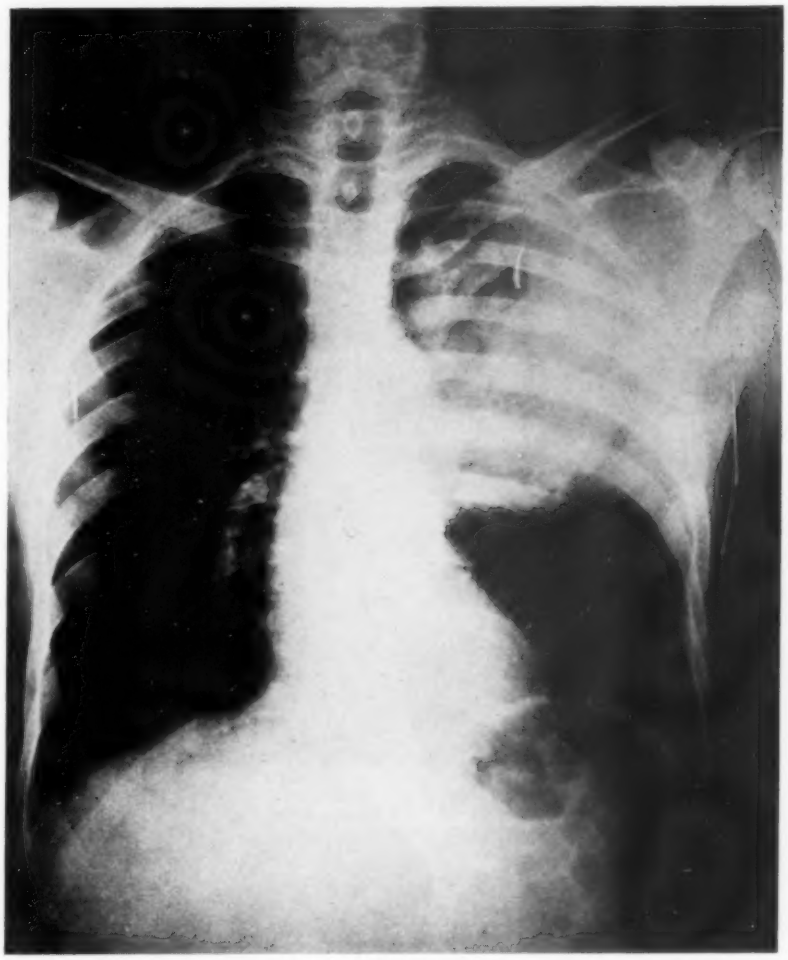

FIG. 5. (12-3-34) *Case 3.* Pneumonic consolidation of left upper lobe; remainder of lungs negative.

tion of exudative tuberculous lesions. The combination of interlobar pleurisy and pulmonary fibrosis occurred so often after the upper lobe pneumonias as to suggest these sequelae as the ordinary sequence of events. It is therefore obvious that the correct interpretation of these lesions is dependent on the history of the antecedent pulmonary infection.

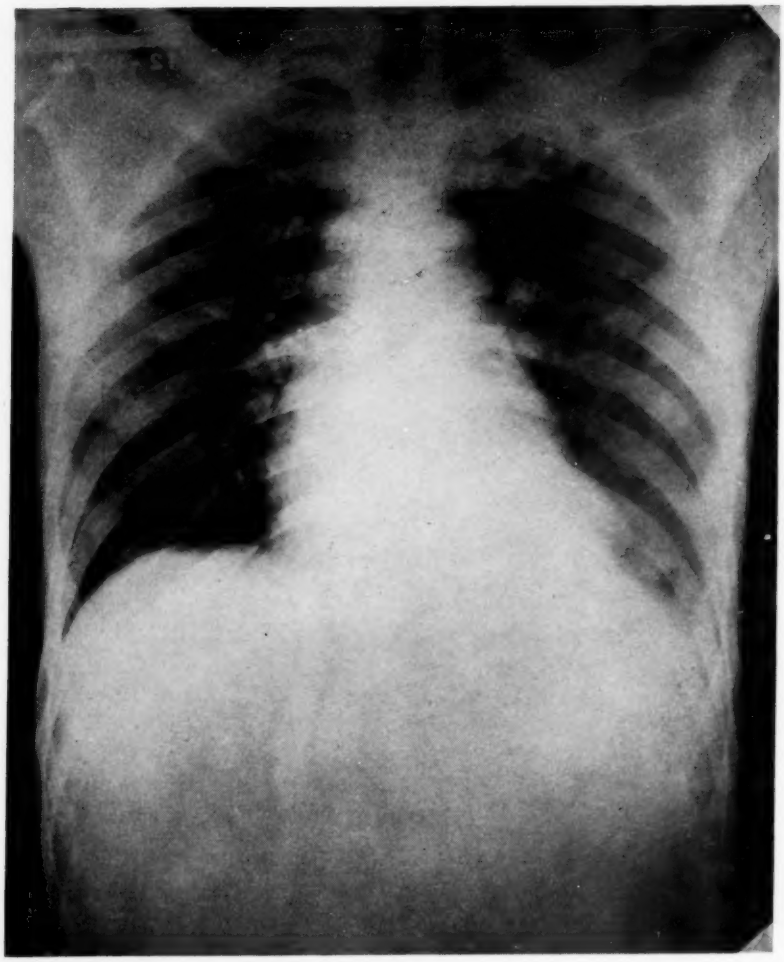

FIG. 6. (12-18-34) *Case 3.* Absorption of lesion; residual interlobar pleurisy and pulmonary fibrosis extending from hilum. (The apparent cardiac enlargement on this film is due to differences in radiographic technic from the previous one).

SUMMARY

1. A statistical study of 180 cases of lobar pneumonia at the City Hospital revealed the presence of upper lobe involvement in twenty-four (13.3 per cent).

2. Involvement of the right upper lobe predominated over that of the left in the ratio of 3 : 1.

3. Examination of the sputum for tubercle bacilli was negative in all instances. Pneumococcus typing was negative for types I–XXXII in half of the cases; in the remainder there was no predominance of any type.

4. The course of illness in most instances was characterized by marked toxicity.

5. The mortality rate of all the cases was 42 per cent. The mortality rate of the cases with isolated upper lobe pneumonia was 21 per cent and of the cases with multiple lobe involvement 70 per cent.

6. The chief difficulties in the diagnosis are due to the frequent absence of physical signs of consolidation and to the similarity to the lesions of pulmonary tuberculosis. Lung abscess and meningitis may have to be considered also in the differential diagnosis.

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HELIOTHERAPY OF TUBERCULOSIS *

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Light therapy, both natural and artificial, is of definite value in the treatment of certain forms of tuberculosis. The clinically effective spectral regions are still to be defined; therapeutically, however, certain advantages are ascribed to sunlight as opposed to artificial sources of light, to one artificial source as against another and even to artificial sources as against the sun.

Empirical evidence still prevails, chiefly because the mode of action of light remains undefined. In the simplest photochemical effects, the physical processes are rarely understood and so the difficulties in biology and therapeutics are understandable. Not even upon the single cell have the effects of light been completely clarified.

Suggestive, however, are the laboratory experiments demonstrating effects upon the reticulo-endothelial system and upon capillary and cellular permeability with their resultant action upon immune processes and upon exchange of colloids and nutrition.

Empirically, however, sunlight represents one of the benefits of outdoor life making for physical and mental well-being. Experimentally in rickets, certain wave lengths of sunshine and artificial sources of light have been shown to be specific. In calcium-deficiency diseases such as rickets and infantile tetany and osteomalacia, ultraviolet energy has proved curative. However, to exaggerate the vital importance of light, either natural or artificial, and to make extravagant claims for it in therapy, employing it to the exclusion of hygienic and dietary regimes, is bound eventually to bring discouragement.

In tuberculosis the nature of the pathologic process must be defined before the indication for light therapy can be stated. Predominantly exudative disease indicates extreme caution, and in pulmonary tuberculosis presents a contraindication.

Benefits from light therapy are undoubtedly obtained by patients suffering from tuberculosis of the bones, articulations, peritoneum, intestine, lymph nodes and larynx when the entire body is exposed to carefuly graded doses of natural sunlight or to radiation emitted by certain artificial sources of light rays. The beneficial results of such irradiation are due not only to ultraviolet rays. The visible and infra-red rays, as well as the conditions of the atmosphere, play a certain part in the therapeutic effect.

In superficial tuberculous ulcerations, healing, if it occurs, is due not to direct death of tubercle bacilli caused by ultraviolet energy, but to a local inflammatory or immune reaction of a nature still unexplained. Such ulcers may also heal during general body irradiation when the ulcer itself is un-

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exposed. Direct irradiation of tuberculous ulcers of the skin, larynx, bronchi and bladder with various sources of ultraviolet has frequently promoted healing; failure may relate to improper dosage, technic or choice of source of radiant energy.

In laryngeal tuberculosis, general body irradiation is often effective. The acute forms, particularly those with edema, contraindicate local irradiation. Vocal silence, bodily rest and electrocautery are much more effective.

Oral and pharyngeal tuberculous ulcers, generally secondary, are most resistant to treatment.

In tuberculosis of the skin, lupus vulgaris alone can be said to respond specifically to light. Scrofuloderma and erythema induratum react favorably at times to general and local exposure, although not as constantly. Papulo-necrotic tuberculids are resistant. Lupus erythematosus does not respond to and may be aggravated by light.

In tuberculosis of the bones and articulations, it is generally agreed that suitable, graded exposure to natural sunlight is most effective in promoting the healing accomplished by orthopedic and other measures. Exposure to artificial sources of radiation is valuable as second choice. Surgery, solar and artificial light therapy, braces, even in some cases the much maligned plaster-of-paris cast, all have their place in the treatment.

It is not to be expected that light therapy will produce new cartilage in place of that which has been utterly destroyed; it does not make the process of fusion less necessary than it has been hitherto, but it can help this develop. It is wrong to expect that its use will bring about regeneration of bone equal to that of a few vertebral bodies when they have been destroyed; but when this has occurred and a gibbous deformity exists, light therapy has aided orthopedic treatment in fusing these diseased surfaces, especially when employed together with postural treatment.

Surgical fusions are less commonly performed on children under 12 years of age. If performed on adults or children, the disease must first show some evidence of retrogression; thus surgery is to help nature.

Indications for surgical intervention may depend on economic and social conditions, the age of the patient, the joint involved, their number and the stage and extent of the disease, involvement of other organs such as the lungs and kidneys, and complicating abscesses or sinuses. Surgical fusion is to be seriously considered in the presence of advanced joint destruction. Restoration of function may occur in the synovial form of joint tuberculosis, even in the presence of large effusions; but complete functional return of motion in a joint is doubtful when the bony parts have been destroyed to a marked degree.

Following operation, patients are still treated from one to two years, and during this period heliotherapy plays an important part. Both mercury arc in quartz, and the carbon arc irradiations, employed as general and local exposures for prolonged periods of time, have proved helpful aids. Small joints yield more quickly to conservative treatment than large ones. The

knee joint is especially refractory, and particularly obstinate are old fistulas of the spinal column, pelvis or hip.

Pulmonary tuberculosis per se is not an indication for light therapy. Uncomplicated exudative pulmonary tuberculosis is a contraindication to light therapy; with proliferative or fibrotic pulmonary tuberculosis, accompanied by elevation of temperature, sunlight or artificial lights, if employed at all, should be used cautiously. Intense sunlight should be avoided, and diffuse daylight or early morning and late afternoon sunlight should be used. Focal or constitutional reactions should be watched for. The indications here resemble those of tuberculin therapy.

In pulmonary tuberculosis, even when quiescent, harm has been done by sunlight exposures, especially with too intense and prolonged irradiations. Solar heat alone, especially in summer, can prove very harmful.

Stationary pleural tuberculosis has often been helped by light therapy. Tuberculous empyemas do not respond.

Genito-urinary tuberculosis deserves a trial of such treatment in combination with other measures. If unilateral renal tuberculosis is diagnosed at the very onset of symptoms and when such symptoms are slight, conservative treatment with light therapy has on rare occasions prevented the need of surgical intervention. As a rule, nephrectomy is indicated.

For unilateral progressive renal tuberculosis or bilateral disease in which the more involved kidney is removed, light therapy is to be advised as a desirable postoperative treatment. It may have a favorable action on the genital organs and the remaining kidney and effectively contribute to the healing of a tuberculous cystitis, whether alone or in association with medical treatment. Light therapy exercises a healing action on the stump of the ureter, which so often shows residual ulceration, resulting in a discharging sinus or a persistent cystitis. It has given excellent results, even with chronic gaping wounds, extensive and deep, and even when covered with ulcerations and tuberculous granulations.

Light is particularly indicated in those not infrequent cases of renal tuberculosis complicated by genital tuberculosis in which the seminal vesicles and prostate are involved, thus often obliging postponement of cystoscopy to avoid trauma of the prostate and the risks of general infection. Therefore, before surgical intervention it is advisable to treat the concomitant lesions with a methodical course of light therapy to make cystoscopy and nephrectomy procedures entailing less risk of dissemination.

In bilateral renal tuberculosis, light therapy is indicated. It may help render the disease quiescent; its occasional analgesic action on ulcerations of the bladder is particularly welcome.

Advanced bilateral renal and bladder tuberculosis has rarely responded to any form of therapy, especially when the patient is cachectic. Postoperative sinuses, especially following nephrectomy, have responded in a large number of cases to light therapy of all forms. Local exposure to ultraviolet rays of circumscribed tuberculous lesions of the urinary bladder has been

shown to yield favorable results, but the method requires special applicating devices and, above all, skilful treatment of the bladder lesion.

Ocular tuberculosis and aural tuberculosis respond infrequently to light. Corneal ulcers and phlyctenular conjunctivitis not infrequently heal under local exposures.

Fistulas are often resistant to such treatment. Postoperative sinuses, in contrast, are most responsive.

Intestinal tuberculosis of both the secondary ulcerative and hypertrophic forms especially indicates light therapy and often is rapidly responsive.

Artificial light and solar therapy, as well as a rich vitamin diet, should be used in most cases, as they frequently relieve the symptoms and bring about recovery.

Excellent results are obtained with the use of artificial sources of radiation, with general exposures either of the mercury arc in quartz, or flaming carbon arc sources. The results depend on factors such as the general status of the patient and the location, extent and nature of the disease in the intestine. Those with far advanced pulmonary and intestinal tuberculosis with little remaining resistance cannot be expected to respond, but intestinal tuberculosis today is healed in many patients, and autopsies have often confirmed this.

The loss of symptoms is frequently surprising, abdominal pain and discomfort disappearing, diarrhea and fever subsiding quickly, and general improvement taking place. Roentgenologic studies show that the intestinal irritability as visualized by roentgen-ray defect clears up entirely in many instances.

In peritoneal tuberculosis, light therapy always deserves a trial first. The serous exudative type generally responds to light irradiation, both in children and in adults. The dry proliferative form, usually adhesive, is more refractory. When there have been ulcerations and large caseous lymph nodes, as commonly seen in children, the results are most unsatisfactory. When the disease is of long standing, healing is more difficult than when irradiation is begun a short time after onset.

The abdominal pain usually disappears rapidly under light therapy, especially in children. Large quantities of ascitic fluid may disappear in a few months.

Tuberculous lymph nodes in the stage of hyperplasia generally heal under solar and artificial light therapy. Occasionally they caseate under light treatment and surgical excision may be indicated followed by postoperative light therapy. Caseous nodes respond although less constantly. Liquefied nodes require aspiration followed by light exposures. Sinuses from draining nodes indicate a course of light treatment. General and local irradiation are essential over periods of many months. Not infrequently roentgen-ray exposures may have to be combined. At times incision into a softening node is necessary.

In tuberculosis, overdosage has produced harmful focal reactions. Light may set up a focal reaction similar to that of tuberculin.

The erythemic reaction is an accurate indicator of skin tolerance. A preliminary exposure of a small area to gauge the minimal perceptible erythema will generally avoid undue burns.

With any form of tuberculosis, light is to be used as an adjuvant only and should be combined with all other indicated forms of therapy. One of these, namely, roentgen therapy, has many restrictions and important contraindications, especially in pulmonary tuberculosis. Its healing effect in certain forms of extrapulmonary tuberculosis has been definitely established, but the limitations must be recognized, dosage carefully regulated, and treatments given only by experts in the field. The mainstays of treatment are still: rest, proper dietary, and hygienic outdoor life.

THE SYNDROME OF EXTRARENAL AZOTEMIA*

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AZOTEMIA signifies an abnormal increase in the non-protein nitrogen (NPN) level of the blood. Normally the blood of a fasting person contains from 25 to 35 mg. per cent of non-protein nitrogen; this includes urea, uric acid, ammonia, amino acid, creatine, creatinine and some nitrogenous substances known as undetermined nitrogen or rest nitrogen. Values for blood non-protein nitrogen over 40 mg. per 100 c.c. are considered abnormal.

Theoretically an azotemia could be caused by an increase of any of these non-protein nitrogen constituents. The amounts of uric acid, ammonia, creatine and creatinine are so small that increases of even several hundred per cent would have but little effect on the total non-protein nitrogen. For practical purposes it can be considered that a noticeable increase in the blood non-protein nitrogen is usually due to alterations in the concentration of urea or undetermined nitrogen or both, and very rarely to changes in the amount of the amino acids.

The high non-protein nitrogen values and the clinical picture of uremia produced by bilateral diffuse and usually progressive kidney diseases, such as glomerular nephritis, nephrosclerosis, pyelonephritis, congenital cystic disease of the kidneys, mercuric chloride poisoning, renal tuberculosis, as well as by obstructive lesions in the lower genito-urinary tract due to tumor, stricture or enlarged prostate gland have been adequately described in medical literature.

On the other hand, but little attention has been directed to the fact that high blood non-protein nitrogen values may result from non-renal disease, or be due to functional or to minor pathologic disturbances of the kidneys which are often reversible under proper therapy. Prerenal or extrarenal azotemia are expressions often used to describe such types of azotemia which are not primarily due to renal disease. Unfortunately these terms imply a lack of participation of renal function in the production of the azotemia. Practically all conditions which are designated as prerenal or extrarenal azotemia are accompanied by functional renal changes and occasionally by minor degrees of renal damage. In many cases the term functional renal azotemia could more properly be applied; but because of long usage the term extrarenal azotemia should be retained. The concept of the syndrome should be expanded, however, to include diminished function of the kidney due to local functional, or even to minor pathologic changes. As will be pointed out later, these pathologic changes are often terminal events initiated

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by purely extrarenal factors and cannot logically serve as the basis for the differentiation of a special group. They have been more or less neglected in texts dealing with kidney disease, and for that reason their importance has been overlooked.

Interest in this problem was stimulated by occasional examples of azotemia unrelated to organic kidney disease. A study of the literature in relation to these cases seems to indicate that the azotemia under these circumstances can be explained on the basis of one or more of six fundamental mechanisms. It is the purpose of this paper to present a review of these mechanisms, and to show by means of analyses of our own cases and of those collected from the literature that they will explain azotemia in all conditions not due primarily to organic kidney disease. An analysis of azotemia from this viewpoint allows a much more rational approach to therapy and clarifies an otherwise very confusing aspect of medicine.

Basic Mechanisms Causing Extrarenal Azotemia

1. *Drop in Blood Pressure.* It has been adequately established that the hydrostatic pressure in the glomerular capillaries furnishes the potential which induces glomerular filtration.[1] The osmotic pressure of the colloids in the blood plasma may be set at about 30 mm. of Hg in normal individuals.[2] The glomerular filtration pressure is represented by the difference between the hydrostatic and the osmotic pressure. The hydrostatic pressure, which is directly dependent on the glomerular capillary pressure, is counteracted by the osmotic pressure of the plasma colloids. The effective glomerular filtration pressure is thus produced by the balance in favor of the hydrostatic pressure. Under normal circumstances the urine pressure in the intracapsular space and tubular lumina is too low to affect appreciably the filtration pressure.[3]

Lassen and Husfeldt [4] studied the effect of changes in blood pressure on the renal function of normal individuals. A fall in blood pressure was produced by means of spinal anesthesia. It was noted that the urine volume diminished directly with the fall in blood pressure until a systolic level of approximately 70 mm. of Hg was reached. As the blood pressure returned to normal, the volume of urine also rose. As a result of their studies, the authors felt that the systolic blood pressure of the peripheral circulation need fall but little below 70 mm. of Hg before the production of urine would cease entirely. It is interesting to note that as the volume of urine decreased, the concentration (specific gravity) of the urine increased. It was concluded that with the lowered blood pressure due to spinal anesthesia, the glomerular function of the kidneys varied directly with changes in blood pressure whereas the tubular function remained unchanged as far as the resorption of water was concerned.

The above holds true for persons with normal blood pressure. It is well known that with advancing years the blood pressure rises and it is not

unusual for individuals past the age of 40 to have hypertension of many years duration. Wilkner [5] raises the question whether or not this habituates the kidneys to depend on a higher filtration pressure, and argues that the threshold at which renal function diminishes in such individuals may be considerably higher than in those with normal blood pressure.

It seems clear, however, that a systemic blood pressure of at least 70 mm. of Hg in normal individuals and perhaps higher in those with hypertension is necessary to maintain adequate renal function.

2. *Hypochloremia and Hyponatremia.* In clinical medicine hypochloremia and hyponatremia are encountered in a wide variety of unrelated diseases. Persistent vomiting, gastrointestinal fistulae, diarrhea, excessive perspiration, rhinorrhea, evaporation from destroyed epithelial surfaces and polyuria are among the common causes of salt loss. More rarely, these blood electrolytes may be lost into body cavities (as in ascites) or into interstitial tissues (as in edema or shock). It is evident that in practically all of these cases, fluid loss accompanies the electrolyte loss. In addition, under experimental conditions and probably rarely in clinical practice dietary salt restriction may result in hypochloremia and hyponatremia.

In the past, attention for the most part has been directed to the chloride level resulting from these conditions. It should be emphasized at this point that sodium loss (in varying degrees) is usually associated with chloride loss. The influence of hypochloremia and hyponatremia on kidney function individually and collectively must be considered.

The frequent association of hypochloremia and azotemia has stimulated considerable experimentation and speculation. The many theories evolved and the contradictory experimental data derived have resulted in much confusion.

Blum and his co-workers [6] believe that urea is retained in the body in order that the osmotic pressure of the body fluids may remain unchanged despite chloride loss. Peters,[7] as well as Kerpel-Fronius and Butler,[8] states that non-protein nitrogen may accumulate in the blood because the patients are dehydrated and are, therefore, unable to excrete the proper volume of urine. Peters [7] and others believe in addition that increased destruction of body proteins may play a part when dehydration is severe.

Certain investigators, Brown et al.,[9] believe that marked anatomical changes in the kidneys, especially the tubules, may be responsible for the nitrogen retention. Haden and Guffey [10] and Mellinghoff [11] ascribe the azotemia to transient renal insufficiency of a purely functional type.

The experiments performed by Haden and Orr [12] in which animals were starved, their duodenum ligated and adequate fluid intake maintained were not conclusive, because Binet and Rathery [13] repeated this work and showed that dehydration, as indicated by polycythemia, was present when this technic was used. The dogs in these experiments lived an average of four to nine days.

Since these results were not conclusive, Glass [14] performed experiments

in which the chloride loss was definitely separated from dehydration. His dogs were given a carefully measured diet which was salt deficient but adequate in all other respects. The development of hypochloremia was also aided by gastric lavage before meals. By this technic Glass succeeded in producing hypochloremia without dehydration or starvation. The blood sodium level was not determined. The water content of the dog's blood plasma remained normal and the animals lived about 20 days in contrast to the much shorter period in Haden and Orr's experiments. Glass found that when the blood chloride loss reached 30 per cent, the urine and stools contained more nitrogen than could be accounted for by that contained in the food. The blood non-protein nitrogen became elevated slightly during the early part of the experiment and rose to very high levels shortly before death. The terminal stage resembled the clinical syndrome of uremia. Accompanying the terminal azotemia there was a diminution in the urinary excretion of nitrogen. This was interpreted as indicating an early rise of non-protein nitrogen due to an increased protein catabolism and followed by a terminal uremia associated with alteration of kidney function. The terminal rise of non-protein nitrogen and death could be prevented if sodium chloride was given to the animals before coma developed. In view of the fact that blood chlorides had to be reduced 30 per cent before these results followed, it was concluded that mild hypochloremia was less important clinically than pure dehydration.

Landis and his co-workers [15] have recently studied the relation between azotemia and hypochloremia and present an explanation supported by laboratory evidence. These investigators showed that when individuals were kept on a diet of known constant nitrogen intake as well as on adequate fluid intake, the average 24 hour urea clearance varied directly with sodium chloride restriction sufficient to produce hypochloremia. No attention was paid to the blood sodium level. The use of the 24 hour urea clearance technic explains their success as contrasted to the non-conclusive results obtained by other workers employing the standard two hour clearance. The level of the blood urea nitrogen rose with a restriction of the salt intake and the urea clearance diminished. In such individuals, treatment with sodium chloride without changing the nitrogen or fluid intake caused the 24 hour urea clearance to increase and the blood urea nitrogen to drop to normal.

In these cases the authors argued that neither dehydration nor oliguria per se explained the changes in renal function since the fluid intake averaged 4500 c.c. and the urinary output 3000 c.c. per day. These experiments were interpreted as indicating that the chloride level of the blood must be considered a factor in renal function entirely distinct from the fluid intake. There is also considerable clinical evidence to support this experimental work indicating that the administration of sodium chloride in selected cases is an aid to renal function.[6, 16]

McCance [17] produced salt deficiency in four persons with normal kidneys. They were given a plentiful intake of water but caused to perspire profusely

and to take a sodium chloride free diet. Azotemia developed in each case. Renal function was studied in one of these persons. The urea clearance was found to be only 60 per cent of normal. Clausen,[18] on the other hand, could not confirm the findings of Landis or McCance. He was unable to demonstrate any correlation between the blood chloride level and the urea clearance test, or between chloride therapy or restriction and the urea clearance test.

Groak [19] in dogs and Clausen [18] with humans produced azotemia by injection or oral ingestion of large amounts of urea. In no case did the blood chloride level change. They were of the opinion that the chloride level as such did not influence nitrogen elimination.

Kerpel-Fronius [20] opened up an entirely new approach to the problem. By means of experiments on rabbits it was shown for the first time that with azotemia due to salt restriction, the important ion was the sodium and not the chloride. Hypochloremia without hyponatremia was produced in one set of animals; in the other the blood sodium was reduced. The animals with hypochloremia, but normal sodium levels, showed no dehydration or azotemia. The group with low blood sodium showed dehydration and azotemia despite an adequate fluid intake.

It remained for Gömöri and Podhradszky [21] to point out the true significance of the above experiments as applied to azotemia in humans. They believe Kerpel-Fronius' experiments are unimpeachable proof that hypochloremia plays no direct part in the development of azotemia; while sodium restriction by leading to dehydration can cause azotemia.

Basic studies by Gamble [22] show that where sodium is lost the body loses the corresponding quantity of water, this loss being from the plasma and interstitial fluids. Gamble's explanation is that the body tries to compensate for the lowered osmosis by a corresponding decrease in water content. In spite of the loss of sodium, the plasma concentration of this ion does not decrease appreciably but the quantity of circulating plasma does decrease. This causes a dehydration similar to direct water reduction. If the blood sodium is low, an increased water intake is of no avail since the newly added fluid does not remain for long in the plasma. Thus, Gömöri and Podhradszky [21] feel that salt deficiency by producing hyponatremia can cause dehydration even though the fluid intake remains adequate. They attribute the resulting azotemia to the dehydration.

From this recent work it is evident that the cause of the confusion with regard to this subject centers in the fact that many investigators have paid attention to only the chloride portion of the problem. It is also evident that both hypochloremia and hyponatremia influence renal function but by different mechanisms. It is well known, as shown by Gamble,[23] that the loss of electrolyte from the body is always associated with fluid loss, and conversely that fluid loss is associated with loss of electrolytes. What has been overlooked is the fact that the electrolytes are not always lost in the same proportions in various body fluids. For example, the patient who vomits loses fluid, much chloride (as HCl) and but little sodium. This results in a

marked hypochloremia but with relatively normal blood sodium level.[23] On the other hand, the loss of pancreatic fluid through a fistula causes a marked hyponatremia with considerably less change in the blood chloride level. The proportional loss of sodium and chloride varies with different body secretions and excretions.

Chloride loss can probably affect renal function only because of the concomitant loss of fluid which is entailed. In this respect, hypochloremia must be considered among the causative mechanisms of extrarenal azotemia. Hyponatremia, on the other hand, seems specifically to produce a diminished blood plasma volume irrespective of the fluid intake or loss. The azotemia which follows sodium chloride restriction is probably intimately linked with the sodium factor.

Aside from the influence on water balance and the level of the nitrogenous products one must not overlook that loss of electrolytes results in a shift of the acid-base balance of the body. If sodium is lost in excess of chlorides (i.e. pancreatic juice) acidosis results. On the other hand, chloride loss in excess of sodium (i.e. gastric juice) results in alkalosis. In this respect, varying degrees of acidosis or alkalosis may accompany the syndrome of extrarenal azotemia.

3. *Dehydration.* That ordinary dehydration may affect renal function has been well established on the basis of scientific investigations and routine clinical experience. Lashmet and Newburgh[24] have shown that under normal conditions the kidneys excrete 35 to 40 grams of solids per day. Each gram of this waste material requires about 15 c.c. of fluid to be dissolved. Therefore even with kidneys working to maximal concentration, at least 500 to 600 c.c. of urine must be excreted per 24 hours to avoid the retention of nitrogenous waste products in the blood. If the kidneys are unable to concentrate to the maximal specific gravity of 1.032, more fluid is required to eliminate the total solids. This has been carefully worked out by them and is shown in the accompanying table.[25]

Maximum Concentrating Ability		Minimum Amount of Water Required to Excrete 35 grams of Waste Material
Specific Gravity		Cubic Centimeters
Normal	1.032–1.029	473
Diseased	1.028–1.025	595
	1.024–1.020	605
	1.019–1.015	850
	1.014–1.010	1,439

In individuals with normal kidneys, the volume of urine is more or less directly related to the fluid intake. This has been adequately and conclusively shown by Coller and Maddock[26] who performed experiments planned to demonstrate the effects of pure dehydration on renal function. In their experiments all other factors known to affect renal function remained con-

stant throughout. The subjects were healthy adults who were permitted light muscular activity. The environment was such that sweating did not result. A diet of low fluid content, just sufficient to cover the caloric requirements, was given. The mineral content of the diet remained constant throughout with an adequate salt intake so that no disturbance of the mineral balance of the body resulted. These subjects were then dehydrated by merely restricting the fluid intake.

The important changes were found in the blood and urine. The nonprotein nitrogen of the blood rose in each case from normal figures of 30 to 32 mg. per cent to 40 to 45 mg. per cent after two to four days of dehydration. The urines before dehydration showed an average specific gravity of 1.015 with volumes ranging from 1200 to 1500 c.c. With dehydration the specific gravities in each case increased to values of from 1.031 to 1.041, while the daily urinary output dropped to 440 to 480 c.c. The urine on the last day of dehydration exhibited traces of albumin, many casts and some red cells. This was an interesting demonstration of the lack of specificity of the presence of albumin, casts and red cells in the urine as indicative of organic renal disease.

Following treatment with fluid alone these abnormal findings in both the blood and urine reverted to normal within one or two days. These experiments seem to indicate that pure dehydration entirely aside from salt restriction or loss may have a definite deleterious effect on renal function. In addition to producing oliguria with its concomitant retention of nitrogen in the blood, dehydration may also cause azotemia by other mechanisms. Meyler [27] in particular has stressed the point that dehydration increases protein catabolism. This has been borne out by other investigators.[28] It should not be overlooked that dehydration by reducing the circulating blood volume may produce shock with its accompanying lowering of the blood pressure. These factors are probably effective only in the severer degrees of dehydration.

Except under strict experimental conditions and rare clinical circumstances, dehydration per se does not occur except in conjunction with loss of body electrolytes. Dehydration without salt loss would, therefore, be expected particularly in instances of restricted fluid intake with normal consumption of food. Possibly to be considered with dehydration is shock. Here blood is shunted from the active vascular tree into stagnant body depots such as the liver, spleen, splanchnic area and sub-papillary capillary plexuses. Aside from the drop in blood pressure, renal function is impaired under such circumstances by the lack of available fluid in the active circulation. The blood passing through the kidneys is dehydrated even though no fluid is lost from the body as a whole.[29]

With dehydration there occurs hemoconcentration which entails an increase in viscosity of the blood.[30] This probably hinders the circulation through the kidney. Medes [31] has shown that decreased blood flow through the kidneys leads to a diminution of the glomerular filtrate. Dehydration

also increases the concentration of total blood protein.[32] The influence of this fact on renal function will be discussed later.

In summary then, dehydration affects renal function by limiting the available fluid for excretory purposes, increasing protein catabolism, diminishing the flow of blood through the kidneys, lowering of the blood pressure, and probably by increasing the colloid osmotic pressure of the blood.

4. *Liver Damage.* Although many of the metabolic functions of the liver were known earlier, it was not until the work of Mann and his co-workers[33] that certain of these functions were definitely established. Of particular interest in relation to the subject under discussion is the experimental proof presented establishing the liver as the site of catabolism of amino acids with the consequent production of urea. Bollman, Mann and Magath[34] in studies on hepatectomized dogs, found that in no case did deaminization occur after the liver had been removed. This was demonstrated by the recovery of amino acid in the blood, urine and tissues of these animals in amounts approximately equal to the anticipated formation of urea. If amino acids were injected into these animals the entire amount of amino acid nitrogen was recovered unchanged in the blood; thus little or no urea is formed in the absence of liver function. In these experimental animals, although the total non-protein nitrogen increased, this increase was associated with an absolute reduction of urea nitrogen and a marked rise in the amino acid nitrogen of the blood.

Clinically this has a definite bearing in cases of advanced liver destruction. Prior to the experimental work of Mann and his co-workers, Stadie and Van Slyke[35] reported a case of acute yellow atrophy which demonstrated these findings. Even more striking, however, is the case of extreme liver destruction reported by Rabinowitch[36] in which the amino acid nitrogen rose to 216 mg. per cent (as contrasted with normal value of from 5 to 8 mg. per cent). No urea could be demonstrated in this instance. From a similar point of view, Stander[37] in reporting a chemical study of chloroform poisoning, found an increase in the total blood non-protein nitrogen with which was associated an increase in the amino acid nitrogen. More recently the studies of Wakeman and Morrell[38] on experimental yellow fever in monkeys demonstrated that in this disease, which is characterized by liver cell damage, the blood urea nitrogen, although increased in most instances, did not increase in proportion to the total non-protein nitrogen. In some cases it showed an actual decrease. The difference in every case was made up chiefly by a rise in the amino acid nitrogen and undetermined nitrogen.

In the past few years there have been many case reports of azotemia subsequent to varying degrees of liver damage in which the rise in total non-protein nitrogen was due to a rise in the urea nitrogen rather than the amino acid nitrogen. Few of these cases, however, have received adequate study from the point of view of various other factors such as hypochloremia, hyponatremia, drop in blood pressure, dehydration and renal function.

This recognized deaminizing function of the liver demonstrates the im-

portance of both amino acid and blood urea nitrogen determination in persons with liver disease. Obviously in the absence of such determinations no true understanding of elevated non-protein nitrogen in liver disease can be obtained.

5. *Protein Catabolism.* Under ordinary circumstances the level of the non-protein nitrogen of the blood is dependent on (1) the adequacy of renal function in eliminating nitrogen in the urine, (2) on the amount of water available to perform this function and (3) on the rate at which protein is broken down in the body.[39] With proper function and available fluid present, an increased rate of protein catabolism is reflected up to a certain point by an increase in urinary excretion of nitrogen. It seems reasonable to assume then that protein catabolism may occur at so rapid a rate that even normal kidneys are ineffectual in removing all of the nitrogen products produced, or too rapidly for normal kidneys to be adjusted immediately to this increased demand. In either case an increase in the level of the blood non-protein nitrogen will result.

The importance of protein catabolism in controlling the level of the non-protein nitrogen of the blood has been emphasized by Peters and Van Slyke.[40] They have pointed out that unless the rate of nitrogen catabolism and the urine volume are known, the blood non-protein nitrogen cannot be utilized as a criterion of renal function. Conversely, it would seem that in the presence of normal renal function and urine volume, an increase in the blood non-protein nitrogen can be associated with increased protein catabolism.

In controlled starvation experiments Lennox et al.[41] demonstrated fluctuations in the blood non-protein nitrogen presumably due to uneven protein catabolism. A previous investigation in animals had been made. Morgulis and Edwards [42] reported an increase of the non-protein nitrogen and blood urea nitrogen at an early stage of fasting which remained at a more or less fixed level until the extreme stage was reached when a much greater increase occurred. The amino acid nitrogen and creatinine remained more or less constant but the undetermined nitrogen rose somewhat. The investigations of both of the above groups indicate that on refeeding, for a time less nitrogen is excreted than ingested. It would seem likely, therefore, that the non-protein nitrogen which leaves the blood in these instances is not excreted but used in building body protein.

Morgulis and Edwards [42] and Mackay and Mackay [28] have shown that when water as well as food is restricted, the rise in the non-protein nitrogen is exaggerated. The latter investigators reported the additional increase of non-protein nitrogen in dehydration experiments further prolonged by intravenous injections of sucrose. Peters and Van Slyke [43] point to this rise of non-protein nitrogen as the result of augmentation of protein metabolism and consider it as an example of toxic destruction of protein. Meyler [27] has presented evidence to indicate that dehydration may be an important factor in increasing protein catabolism. It is also considered by some [27] that

acidosis may play a similar rôle. Glass,[14] in the experiments previously mentioned, was able to show that chloride (? salt) loss leads definitely to some degree of protein destruction.

In a series of experiments on the effects of protein intoxications and injury of body protein Cooke and Whipple [44] and their collaborators [45] point out the occurrence of high non-protein nitrogen with sterile abscess formation, septic inflammations such as pleurisy, pneumonia and peritonitis in experimental animals; and in man with septicemia, peritonitis and pneumonia. In these works the azotemia was accepted as an indication of increased protein catabolism in the presence of anatomically normal kidneys.

Recently Lurje [46] in continuing the investigations on protein metabolism in instances of severe surgical trauma in cases with intact innervation of the liver has demonstrated an increase in the amino acid nitrogen of the blood which appears to be due to a reflex provoking endogenic breaking down of proteins.

Cases reported by Rackemann, Longcope and Peters [47] of nitrogen retention occurring in the course of acute allergic states are very interesting in view of the interpretation that these are due to some degree of tissue injury. Also, Hashimoto [48] has shown that with histamine intoxication similar changes in the blood chemistry take place. Although protein metabolism is believed to be partly responsible for this change, it must not be forgotten that at autopsy Hashimoto [48] found marked degenerative changes of the tubular epithelium.

In extensive studies of nitrogen metabolism as affected by iodides Grabfield and Prentiss [49, 50] determined that iodides caused an increased nitrogen excretion probably resulting from increased nitrogen catabolism. In the case of potassium iodide, however, the deleterious effects of potassium on kidney function must be remembered.

To recapitulate, there seems to be evidence to indicate that the factors of starvation, dehydration, acidosis, salt loss, infections, fever, trauma, allergy, and certain drug intoxications may all be associated with increased protein catabolism. There is some doubt, however, as to whether these factors operating independently can produce a significant degree of azotemia. It is perhaps better to consider them as contributory factors, since under actual clinical circumstances, they are usually interrelated with other mechanisms capable of producing azotemia.

6. *Local Renal Disturbance.* That progressive organic kidney disease may alter renal function is so well known that it requires no further comment. On the other hand that minor changes in renal tissue may cause alterations in function which are often reversible is not so well appreciated. These may occur in a wide variety of unrelated systemic diseases, and are characterized by diversified change in the kidney parenchyma and resultant alterations in renal function. Only too often are these minor changes noted at autopsy with no attention paid to them in explaining physiological dis-

turbances. Likewise, it is often overlooked that disturbances in the kidney of a functional nature can result in diminution of excretion of urine.

The factors which influence the output of the urine will be briefly reviewed in order that the concept under consideration may be more clearly understood. Cubitt,[3] in a recent review on renal physiology summarizes them as follows: (1) The urine pressure, (2) Changes in the secretion-reabsorption activity of the tubule cells, (3) The blood pressure in the glomerular capillaries, (4) The area of the capillary bed from which filtration is taking place, (5) The osmotic pressure of the colloids in the plasma of the blood contained in the glomerular capillaries, (6) Nervous control and (7) Hormonal control.

Whether changes in the secretion—reabsorption activity of the tubule cells can account for changes in renal function is still problematical. It is possible that the activity of the tubule cells may be changed by alteration in blood supply, pressure of urine within the tubules, and microscopic changes within the tubule cells. For a similar reason the control of the area of the capillary bed from which filtration can take place must be disregarded. It can not be measured readily in the living, nor can it be seen in anatomical material. It is evident that the control of this area must depend on systemic blood pressure, nervous influences, presence or absence of chemical substances or hormones present in the blood, and on the state of relaxation and contraction of the afferent and efferent arterioles controlling the blood supply to the glomeruli. Since the kidney normally needs but a small fraction of its total glomeruli for normal renal activity, it seems unlikely that anything except a diffuse change would result in loss of renal function severe enough to cause nitrogen retention. Because the afferent and efferent arterioles are under nervous and chemical control it is conceivable that a widespread loss of effective filtrating area could result through some humoral stimulation or nervous reflex.

The principal function of the renal nervous control is regulation of the vasomotor functions with vaso-constrictor action predominating. Any stimulation of the splanchnic trunk (either directly or perhaps indirectly from a distance by reflex action) lessens the amount of urine secreted. Conversely, depression or section of the splanchnics increases the amount of urine.[51] There is no good evidence that nerves carry secretory fibers.[51] The nature of reflex anuria is obscure and will be discussed in detail later.

The effect of the systemic blood pressure on urinary function has already been mentioned. It was pointed out that the effective filtration pressure depends on the difference between the hydrostatic pressure of the blood due to the general arterial blood pressure, and the counter pressure due to the osmotic tension of the serum proteins. This holds true as long as the urine pressure on the tubular side of the glomerular membrane is not increased. Normally the intracapsular urinary pressure is nil and can be disregarded. Any rise of the urine pressure in the intracapsular and tubular spaces, however, interferes with the effective filtration pressure. Such in-

creases in urine pressure can result from partial or complete obstruction of the kidney tubules.

Under normal circumstances the colloid osmotic pressure of the blood rarely exceeds 25 to 30 mm. of Hg.[2] This pressure depends chiefly upon the blood proteins. It is well known that in severe states of dehydration hyperproteinemia results.[32] Görömi and Podhradszky [21] measured the colloid osmotic pressure in animals before and after dehydration. The average normal for cats before dehydration was 33 mm. of Hg. Even though the albumin-globulin ratio reversed with dehydration, the osmotic pressure of the blood proteins increased, reaching in some cases over 60 mm. of Hg. They considered the hyperproteinemia due to dehydration an important factor operating within the kidney in the extrarenal azotemic syndrome. This effect is obtained by counteracting the glomerular filtration pressure.

Changes in the renal tubules are not specific and may occur in the course of a wide variety of clinical conditions. Not only are the clinical pictures with which they are associated variable, but often the changes themselves vary from microscopic degeneration to evidence of gross necrosis and, on occasion, are entirely absent. In addition, obstruction can occur from precipitation of material present in the glomerular filtrate, thus occluding the tubular lumina.[52] It would appear that these changes are not necessarily progressive in nature, and, as a rule, disappear as the patient recovers from the systemic condition with which they are associated. They are noted at autopsy only when a patient dies during the course of disease prone to produce tubular damage. At this time changes varying from cloudy swelling to actual necrosis of tubular epithelium with inspissation of granular debris in the lumina of the tubules may be noted.

Experimentally it has been shown that advanced as these changes may be, if given the opportunity, regeneration and presumably return of normal function will take place.[53] These tubular changes (even though anatomical) must be considered as appertaining to the mechanisms of this syndrome, since they are often produced by the prolonged presence of factors of purely extrarenal origin. The widespread presence of such changes can cause the kidney volume to be increased and the capsule of the kidney to be distended. At autopsy, such kidneys are increased in weight and are grossly edematous and swollen, with bulging of the cortex when the capsule is cut.

These changes in the anatomical structures of the tubular cells invariably result either in an increase in the size of the cells or in the extrusion of cellular debris into the tubular lumina. The end result in either case is a diminution of tubular patency which in turn increases the urine pressure within the tubular and intracapsular space. If the increase in urine pressure is sufficient it may counteract effective filtration through the glomerular capsule and lead to retention of nitrogenous waste products in the blood.[3]

The cause of tubular changes is not clear. One possible explanation is illustrated by the interesting series of animal experiments performed by

Hashimoto.[48] He showed that after the intravenous injection of 1 to 3 mg. of histamine dichloride evidence of intoxication could be expected. This toxicity was associated with a rise of the blood non-protein nitrogen, fall of blood pressure, and markedly diminished urinary flow. The post-mortem findings were definite and characteristic, consisting of diffuse degenerative changes in the tubular epithelium with no changes in the glomeruli. One cannot fail to recognize the resemblance between this picture of histamine shock as described by Hashimoto, and that of extrarenal azotemia as depicted in this paper. In view of the possibility that histamine, or a histamine-like substance, may be liberated in many shock-like states, it seems more than justifiable to include histamine as one of the possible factors in the production of extrarenal azotemia.

Aside from these anatomical changes in the tubular epithelium another mechanism may lead to an increase in urine pressure with a consequent diminution in renal function. It should not be overlooked that the systemic venous pressure when increased may lead to congestion and edema of the kidney. The capsule of the kidney prevents renal distention beyond a certain volume. Therefore, as venous pressure rises, the intrarenal pressure is also increased and is transmitted equally in all directions. At a certain point this will necessarily result in compression of the tubules and thereby raise the urine pressure within the intracapsular space. This in turn diminishes the effective filtration pressure and may lead to oliguria and azotemia. In addition to its effect in increasing the urine pressure, venous congestion influences urinary function by diminishing the blood flow through the kidney and by producing an anoxemia.[54]

One cannot overlook the possibility that renal function may be partially influenced by hormonal control. Of the various endocrine glands in the human body, there is evidence that specific hormones from the pituitary gland and the adrenals exert such an influence.

The diuresis inhibiting action of posterior pituitary lobe extract in man has been recognized for many years. Starling and Verney produced this effect on an isolated kidney and it has further been shown that the effect is not altered by denervation of the kidney. This indicates that the antidiuretic effect of posterior lobe extract is primarily on the kidneys. Although the exact site of action in the kidneys is still undecided upon, the bulk of the evidence seems to indicate that the antidiuretic action of this hormone is due to increased reabsorption of water without much change in the rate of glomerular filtration.[55] The indiscriminate use of pituitrin, especially in postoperative cases where the fluid balance is readily disturbed, may well be a significant factor in producing azotemia.

Loeb et al.[56] have demonstrated that adrenal cortical substance influences sodium excretion. This has been well substantiated by others. In considering the azotemia found in Addison's disease, Loeb and his co-workers [56] were unable to explain it by purely extrarenal factors. From the evidence on hand, they postulated: "that the adrenal cortical substance acts on the

kidney to control the excretion not only of sodium but also of urea. In adrenal insufficiency, the rate of salt excretion is increased while urea elimination is retarded." This hypothesis is attractive in view of the adrenal damage commonly found in severe infections and certain toxic conditions (i.e. burns) in which azotemia is not uncommon.[57] It is evident that a disturbance in adrenal physiology may at times play a rôle in the initiation of extrarenal azotemia.

Discussion. It should be kept in mind that these six mechanisms, although presented separately, are interlinked and often interdependent. This method of presentation serves merely to clarify an otherwise extremely complex exposition. The interrelationship of these mechanisms is well exemplified by a hypothetical situation. In a patient who has a severe diarrhea, there is an entailed loss of fluid, sodium and chloride with resulting dehydration and diminution of the circulating blood volume. There is then an associated fall of blood pressure. Starvation, dehydration, fever and hypochloremia would increase protein catabolism. If the patient is severely toxic, renal tubular damage may supervene. This combination of circumstances brings on the extrarenal azotemic syndrome. One can imagine many situations in which the combinations of mechanisms would be much simpler and others where they would be more complex.

The concept of extrarenal azotemia cannot be rationally expounded without considering factors operating locally in the kidney. Renal tubular damage or tubular occlusion may be found terminally in many cases with azotemia primarily due to extrarenal factors. It is not, however, an invariable finding. For this reason such cases can more rationally be placed in the extrarenal syndrome than segregated in some unsatisfactory subgroup of organic renal disease.

The very term " extrarenal " is a poor one, but serves as a useful designation to separate this type of azotemia from that due to the well recognized organic renal diseases. All the extrarenal factors (no matter how far distant from the kidney may be their source) produce, either directly or indirectly, some effect which operates directly in the kidney.

Pathogenesis of Extrarenal Azotemia in Various Clinical Conditions

Azotemia occurs frequently in clinical conditions other than those associated with organic kidney disease. This type of azotemia is extrarenal in origin. While it is more commonly seen in certain clinical states, it may be present in any disease in which the above mentioned mechanisms are operative. An attempt is made here to indicate the pathogenesis of extrarenal azotemia by analyzing the responsible mechanisms in a series of chosen clinical conditions which are illustrated in part with our own case histories. A similar approach is possible under any circumstance in which azotemia occurs in the absence of organic kidney disease.

1. *Coronary Thrombosis:*

Case 1. A 63 years old man was admitted to the Evans Memorial Hospital with a two day history of precordial distress, faintness, vomiting, restlessness and dizziness. Significant physical findings included cyanosis, slight dyspnea, a few râles at the bases of the lungs, distant heart sounds of tic-tac quality, and a pulse rate of 140. Blood pressure was 90 mm. of Hg systolic and 70 mm. of Hg diastolic. Temperature was 100° F.

The first urine specimen had a sp. gr. of 1.025, a slight trace of albumin, no sugar, and a few leukocytes and casts per high power field in the sediment. Subsequent specimens of urine were of even higher specific gravity. The leukocyte count was 20,000 with 85 per cent polymorphonuclear neutrophiles. The electrocardiographic findings were typical of an acute coronary occlusion. The patient rapidly grew worse and died two days after entry. The blood pressure and pulse were unobtainable for 24 hours before death.

The pertinent laboratory data are summarized in table 1.

TABLE I

Date	B.P.	Blood N.P.N. mg. %	Blood Urea N	CO_2 Combining Power	Whole Blood Chlorides	Sp. Gr. of Urine
1/6/37	90/70	45	20	57	433	1.025
1/7/37	?	71	38	49	370	1.030

The autopsy revealed the presence of considerable sclerosis of the coronary vessels with massive infarction of the left ventricle. Grossly the kidneys were normal. Microscopically the glomeruli were normal, but the tubular cells were swollen, often acidophilic, with some of the lumina containing granular debris.

The occurrence of azotemia in coronary thrombosis is not often mentioned but Steinberg [58] found the non-protein nitrogen of the blood to be over 40 mg. per cent in 20 of 31 cases. An analysis of the mechanism of the disease readily explains this frequency of azotemia. A drop in blood pressure, even to shock levels, is common. The effect of this on renal function has already been discussed. The other major factor contributing to azotemia is the diminution in the volume of circulating blood. This may be due in part to vomiting, sweating or to fluid restrictions. The chief cause, however, as shown by Fishberg et al.[59] is the redistribution of the blood, whereby a smaller fraction of the total volume of blood in the body remains in active circulation, and a larger fraction stagnates in dilated capillaries and perhaps within the blood depots. In other words, the features of the shock syndrome are prominent. This, by limiting the fluid available for renal excretion, further influences the retention of nitrogenous waste products.

The urinary findings have been strikingly presented by Steinberg.[58] Most urines showed high concentrations, specific gravities of 1.020 or higher, with the presence of albumin, casts and occasionally red blood cells. In a few instances urinary suppression was complete. Oligurias with 24 hour volumes of 500 c.c. or less were common.

Starvation, destruction of body protein, toxic damage to renal tubular cells and venous congestion due to heart failure may at times play lesser rôles in producing the azotemia.

As shown by Steinberg,[58] and by analysis of the above factors, it is obvious that a blood non-protein nitrogen which remains elevated or continues to rise is of ill omen and offers a poor prognosis. Serial blood non-protein nitrogen studies and urine analyses should be included along with the electrocardiogram, white blood count and sedimentation rate in evaluating cases of coronary thrombosis.

Case 1 is a classical example of azotemia due to coronary thrombosis. Postmortem examination showed that the kidneys were essentially normal for this person's age, except for the recent tubular changes. Vomiting, drop in blood pressure and the shock syndrome were the responsible factors. The urine with its high specific gravity of 1.025 to 1.030 and the presence of albumin, cells and casts was characteristic. There was in addition a mild hypochloremia. Tubular damage was probably minimal.

2. *Alkalosis:*

Case 2. A 31 year old man was admitted to the Boston City Hospital with a history of a duodenal ulcer of several years' duration. A dietary regime and alkaline powders had afforded relief until about eight months previously when symptoms recurred. The patient then resorted to daily self-induced vomiting. He became nervous and irritable, and developed vertigo, nocturia and shooting pains and aches in both legs.

Physical examination showed epigastric tenderness, tenderness of the leg muscles and active reflexes. His blood pressure was 120 systolic and 90 diastolic.

The history, examination, laboratory data and course are typical of alkalosis.

The significant laboratory data are given in table 2.

TABLE II

	N.P.N. mg. %	Plasma Chlorides mg. %	CO_2 Comb. Power Vol. %	P.S.P. %	Urine Sp. Gr.	B.P.	
						Systolic	Diastolic
4/13	130	430	82	6	1.010	120	90
4/14	120	485	65		1.014	120	80
4/15		500					
4/20			60				
4/22	98	508	45	10			
4/29	82	520	40		1.011	120	80
5/30	63	585	42	20	1.012		
6/24	50	588	42	28	1.010	120	80

The patient was given four liters of fluid daily with 30 grams of sodium chloride. Alkalies were omitted. The vomiting ceased after one week, and the nocturia disappeared after the first month.

The syndrome of alkalosis is characterized chemically by azotemia, hypochloremia, and increased carbon dioxide combining power. It may oc-

casionally occur solely from excessive loss of hydrochloric acid (vomiting of gastric juice). The blood sodium level may be normal. Ingestion of alkali by persons with organic renal disease readily causes alkalosis. In addition ingested alkaline salts may cause alkalosis if the fluid and chloride balance of the body are disturbed by vomiting, hematemesis, or excessive sweating. This phase of the subject is discussed at length elsewhere by Jeghers and Lerner.[60] In addition, it has been shown that severe alkalosis can cause damage to the tubules of the kidney, thus further diminishing renal function.[9] When tubular damage occurs, loss of ability to concentrate the urine may follow. The process seems to be reversible if treatment is prompt.

It is uncertain whether the ingestion of alkalies can cause renal impairment in a person with normal kidneys unless some auxiliary mechanism be present. A case reported by Steele [61] suggests that it can. A man, aged 52, had ingested alkalies for years. There was no evidence of renal disease prior to this therapy. Renal failure developed without clinical symptoms of alkalosis. The blood urea nitrogen rose, phenolsulphonephthalein excretion and urea clearance were diminished, urinary concentration was fixed at a sp. gr. of 1.010 and albumin casts and red cells were present in the urine. Withdrawal of alkalies caused a prompt drop in blood urea nitrogen. It was not until three years later that urinary function was entirely normal.

Case 2 is an interesting example of alkalosis. An admission to the hospital four years before had shown normal renal function. The ingestion of alkaline powders, in the presence of diminished chloride and fluid due to vomiting initiated the syndrome. Renal tubular damage resulted. Even when the blood chemical findings had returned to normal, the phenolsulphonephthalein excretion was still low and the urine specific gravity fixed at a low level. This patient was seen one year after discharge; at this time he had regained normal renal function, including ability to concentrate.

3. *Pyloric Obstruction:*

Case 3. A 61 year old man was admitted to the Boston City Hospital, complaining of anorexia, pain in the left flank, small nodules in the skin and loss of weight.

Scattered pea-sized, non-tender nodules were made out in the subcutaneous tissue of the face, neck and back. A walnut-sized nodule was palpable in the left supraclavicular fossa. The blood pressure was 175 systolic and 100 diastolic. A vague sense of resistance was made out just above the umbilicus.

The kidneys showed an ability to concentrate to a maximum of 1.033. On occasions a slight trace of albumin was noted, otherwise the urines were negative. The non-protein nitrogen was 35 mg. per cent on admission, but two days later the patient developed intractable vomiting and the non-protein nitrogen rose to 125 mg. per cent. The plasma chlorides fell from 570 to 426 mg. per cent. Death occurred one week after admission. The blood pressure remained well sustained.

The autopsy revealed extensive carcinomatosis with metastases to the vertebrae, pelvis and skin. The primary lesion was an obstructive pyloric carcinoma. The

combined weight of the kidneys was 270 grams and they were grossly and microscopically within normal limits.

That azotemia may complicate pyloric obstruction has been well shown, both experimentally and clinically.[9] The above case is a good example of azotemia due to this cause. The mechanism is easy to understand. Vomiting causes loss of fluid and of chloride. The effect of this on renal function has already been discussed. In this particular case, the renal tubules were normal at autopsy. Occasionally if the syndrome is prolonged, tubular damage may result with concomitant loss of power to concentrate the urine. With the tubules normal, as was the case here, the urine is highly concentrated and scanty.

4. *Peritonitis:*

Case 4. A 59 year old woman was admitted with a known history of a peptic ulcer of ten years' duration. Three days before she had developed sudden epigastric pain, abdominal distention and vomiting. The vomitus became blood-streaked, probably from retching.

On entry the patient was semi-stuporous; the skin was dry; râles were heard at both bases, and the blood pressure was 60 systolic and 10 diastolic. The abdomen was distended and tender, most markedly so in the right lower quadrant. Definite tenderness was noted on rectal examination. The temperature was 97° F., the pulse 120, and the respirations 30.

After admission the temperature rose to 102°, and she lapsed into coma. The urinary output was only 40 c.c. in 24 hours despite the fact that fluids were forced. The patient died four days after admission.

The specific gravity of the urine was 1.019, a very slight trace of albumin was noted and a moderate number of leukocytes and rare granular casts was seen in the sediment. The non-protein nitrogen on admission was 55 mg. per cent and rose to 100 mg. before death.

The autopsy confirmed the clinical impression of peritonitis resulting from a ruptured duodenal ulcer. The combined weight of the kidneys was 240 grams. Microscopic examination revealed the presence of a minimal degree of nephrosclerosis and considerable swelling of the tubular epithelium which in some places was desquamated.

In peritonitis we have many mechanisms operating to produce an azotemia. Dehydration is caused by vomiting and shift of available circulating blood volume. Salt loss will usually accompany this fluid loss. Blood pressure is often low. Fever, infection, and starvation increase protein catabolism. In addition, it is not unknown for the tubular epithelium of the kidney to show changes varying from swelling to actual necrosis with plugging of the tubular lumina. This adds a local renal factor to those of extrarenal origin. Case 4 shows how all these factors can be operative in a single patient.

5. *Liver-Kidney Syndrome.* There has been considerable discussion in the recent literature concerning the so-called liver-kidney syndrome.[62, 63] Chief interest has been centered in the attempt to find the noxious agent which is supposedly elaborated by a damaged liver and which secondarily

affects renal function.[64] It is obvious that the azotemia in many of the cases of this syndrome which have been reported, can be explained on the basis of the mechanisms discussed in this paper. A recent paper by Lichtman and Sohval [65] emphasizes this point of view. The following two cases illustrate this point.

Case 5. A 35 year old woman was admitted to the Boston City Hospital, with a history of eructations and of vomiting once or twice weekly for six months. Jaundice and weakness had been noted for two weeks, and the patient had become delirious 24 hours before her admission.

Physical examination showed a markedly icteric skin with scattered petechial hemorrhages. The tongue was dry. The liver edge was not felt but the spleen was palpable 1 cm. below the costal margin. Respirations were 12, pulse 104 and the temperature 102° F. Blood pressure was 70 mm. Hg systolic and 50 mm. diastolic.

The specific gravity of the urine was 1.032; there was a slight trace of albumin. The sediment was loaded with granular and hyaline casts. The patient could not be roused from her coma and died 12 hours after admission. The blood non-protein nitrogen was 250 mg. per cent.

The autopsy revealed petechial hemorrhages in all the serous surfaces. The liver was very small, weighed 680 grams, and showed the characteristics of acute yellow atrophy. The combined weight of the kidneys was 260 grams. Bile staining, and degeneration of the tubular epithelium, and hemorrhages about the tubules of the cortex and medulla were noted microscopically.

It is unfortunate that complete chemical studies were not available in this case, but in view of the very high non-protein nitrogen and the extremely small liver, certain deductions are warranted. The azotemia here may well have been mostly amino-acid nitrogen retention due to massive liver destruction. This case closely resembled the one reported by Rabinowitch [36] which showed a liver weighing 650 grams, dehydration and fall in blood pressure.

Case 6. A 67 year old man was admitted to the hospital because of the development of nausea and vomiting one and one-half weeks after an injection of neoarsphenamine. It had also been noted that the skin had become yellow and the urine dark in color.

On physical examination a moderate degree of jaundice was observed. The abdomen was tympanitic and distended and the liver edge was made out 8 cm. below the costal margin. The temperature was 98° F., the pulse 100 and the respirations 18.

The maximum specific gravity of the urine was 1.027. A very slight trace of albumin was present and an occasional granular cast was noted in the sediment.

The patient gradually became worse, and the liver edge seemed to recede about 1 cm. daily. At the end of a week he developed generalized edema, sank into a quiet coma and died. The pertinent laboratory findings are given in table 3.

The autopsy showed an extensive hepatitis presumably due to arsphenamine. The combined weight of the kidneys was 360 gm. Microscopically they showed bile staining and a moderate degree of degenerative change in the tubular epithelium.

In this case the azotemia was due to retention of urea nitrogen. The amino acids remained normal. Dehydration was minimal. The single chloride determination gave a high normal value. The low level reached

TABLE III

Date	N.P.N. mg. %	Blood Urea N mg. %	Amino Acid mg. %	Uric Acid mg. %	Plasma-Chlorides mg. %	T.P. gm. %	Alb. Glob.		B.P mm. of Hg	
							gm.	%	Systolic	Diastolic
11/9	30								115	70
11/18	74	34		2.5	671	6.8	2.9	3.9	70	50
11/20	60	44.9	7.2			7.0			40	20

by the blood pressure was striking. Autopsy showed evidence of mild damage to the tubular epithelium of the kidneys.

6. *Yellow Fever.* In a series of careful studies on the chemistry and metabolism in experimental yellow fever Wakeman and Morrell [38] pointed out that, although the blood urea nitrogen increased in most instances, it did not increase in proportion to the rise in the total non-protein nitrogen. In some instances the urea fraction was actually decreased, a proportionate increase occurring in the amino acid nitrogen and also in the " rest nitrogen." The terminal increase in the non-protein nitrogen was further accentuated in most cases as a result of late shock. In such instances the blood pressure dropped markedly and oliguria or anuria developed. A part of the terminal increase in the azotemia may also be due to the high rate of protein destruction characteristic of the disease. The ability of the kidneys to produce urine of normal concentration seems to be almost unimpaired throughout the disease.

7. *Gastrointestinal Hemorrhage:*

Case 7. A 50 year old man was perfectly well until 10 hours before admission to the hospital when he had sudden nausea and began vomiting blood. About a quart of blood was vomited by the time he was admitted to the hospital. A history of chronic alcoholism was obtained.

On admission the patient was obviously in shock, the pulse was weak and thready and the respirations were 26 per minute. The blood pressure was 95 systolic and 55 diastolic. The remainder of the physical examination was not remarkable.

The patient was given morphine and intravenous fluids. He continued to vomit blood. On the second day he was given a transfusion of 500 c.c. and saline clyses, and seemed somewhat improved. On the fourth day, however, he began vomiting again, the temperature rose to 100° F. and he died.

The pertinent laboratory findings are given in table 4. The urines showed a specific gravity of 1.014 and were otherwise negative.

TABLE IV

Date	Hgb. per cent	R.B.C. in millions	W.B.C.	N.P.N. mg. per cent
7/29/34	70	4.2		
7/30/34	69	3.2	21,800	81
8/2/34	50	2.4		218

The effects of blood loss on the level of the blood non-protein nitrogen were clearly indicated by Taylor and Lewis[66] and later by Buell.[67] More recently, particularly in Denmark,[68] this problem has received considerable careful attention. It seems clear that at times massive gastrointestinal hemorrhage can cause a marked azotemia.

Here, as in other conditions, several factors come into play which may affect renal function. Large hemorrhages are associated with varying degrees of dehydration, salt loss, lowering of blood pressure and hemoconcentration. It has in addition been postulated that the reabsorption of digested blood from the gastrointestinal tract could directly influence protein metabolism.[69]

Often in hemorrhage, the problem is not one of blood loss particularly, for the quantity of blood lost may be considerably less important than the resultant degree of shock with fluid shunted from the active vascular circuit into stagnant depots. Not to be overlooked is the starvation and fluid restriction that such persons are subjected to as part of the treatment of the bleeding.

8. *Postoperative:*

Case 8. One week before admission this 42 year old woman noted pain in both lower quadrants which increased in severity. Anorexia and nausea developed, with some burning on urination.

On physical examination tenderness and spasm of the lower abdomen were noted. A doughy mass in the posterior cul-de-sac was palpable during the course of a painful rectal examination. The temperature was 97° F., pulse 100 and respirations 25. The leukocyte count was 25,000 with 93 per cent polymorphonuclear neutrophiles.

The specific gravity of the urine was 1.020; a trace of albumin was present; a moderate number of leukocytes and a few coarse granular casts were seen in the sediment. The non-protein nitrogen was 57 mg. per cent.

A laparotomy, performed two days after admission, disclosed a bilateral purulent salpingitis with peritonitis. The fallopian tubes were removed and the abdomen drained. Two days after operation the temperature rose to 101°, the pulse remained at 100, but the respirations rose to 30. On the eighth day the patient developed a generalized convulsion and thereafter frequent muscular twitchings were noted. The non-protein nitrogen rose to 240 mg. per cent; pain and swelling of the right parotid appeared, and the patient lapsed into coma and died.

The autopsy revealed the presence of peritonitis and bilateral bronchopneumonia. The combined weight of the kidneys was 395 gm. The capillaries were engorged, the tubular epithelium swollen and, in places, desquamated. Many of the tubules were distended with amorphous albuminous material and some of the lumina contained hyaline casts.

Postoperative rises of blood non-protein nitrogen are extremely common if one performs routine blood chemistries. This aspect of the subject has been recently discussed by Derow.[70] The significance of insufficient fluid intake, lowered blood pressure, pituitrin medication, vomiting and increased body protein destruction was emphasized. Not mentioned but of interest, is the possible presence of renal tubular damage which would add a local anatomic renal factor to the above mentioned impairments of physio-

logical functions. Case 8 illustrates many of these mechanisms in a single patient. Of note also in this case were the muscular twitchings which are classically seen in uremia.

It is obvious from the data on hand that in all postoperative patients daily examination of the urine, with special reference to the 24 hour volume and specific gravity, should be performed. Periodic blood chemical examinations would be of additional aid. From these, one could detect an azotemia long before it became manifest clinically and could plan the therapeutic procedures more efficiently. Pituitrin should be used with due caution.

9. Congestive Cardiac Failure:

Case 9. A 32 year old white man, admitted to the Boston City Hospital, had noticed progressive dyspnea, edema of ankles, cyanosis and a feeling of distress in his abdomen for 16 months. The past history was not satisfactory. Physical examination revealed a well nourished man, markedly cyanosed. The peripheral veins were distended. The lungs were free of râles. The heart was enlarged, the pulmonic second sound was accentuated and a rough systolic murmur and thrill were noted over the apex. The rhythm was regular and the pulse was 88. The blood pressure was 118 mm. Hg systolic and 75 mm. diastolic. The liver was enlarged 6 cm. below the costal edge and was tender. There was soft pitting edema of legs, buttocks and sacrum.

The urine contained an infrequent slight trace of albumin and 1.030 represented the maximum specific gravity. The hemoglobin was 93 per cent (Sahli), erythrocytes numbered 5.5 million and the leukocytes 8,300.

During the patient's hospital stay, the peripheral edema and cyanosis increased, the liver enlarged and eventually showed a systolic pulsation as did the distended neck veins. The patient's condition grew steadily worse, and four days before death jaundice appeared which gradually increased in intensity. The blood non-protein nitrogen on admission was 31 mg. per cent but rose to 100 mg. per cent two days before the onset of jaundice. The blood pressure level was maintained until the end. After a month, the patient sank into a deep coma and on the day before his death uremic snow was noted on the cheeks and sides of the neck. The urinary output was diminished but the specific gravity remained at 1.030.

The autopsy revealed rheumatic heart disease with mitral stenosis, tricuspid regurgitation and right ventricular hypertrophy. Multiple pulmonary infarcts were present. Chronic passive congestion of the liver, spleen and lungs was noted. The combined weight of the kidneys was 285 gm. The width of the cortex was 7 mm. Microscopically the kidneys were normal except for congestion.

Numerous studies of renal function during heart failure have been made.[71, 72] Foster [73] demonstrated that an increased non-protein nitrogen of the blood may result purely from circulatory disturbances. In a study of eight cases of congestive heart failure he found an average non-protein nitrogen of 61 mg. per cent with extremes of 40 and 90 mg. per cent. Four of these cases were examined after death and showed no evidence of renal disease.

Sustained high venous pressure can cause congestion of the kidneys. Even normal kidneys can accommodate for this congestion only to the limit of the distensibility of their capsules. Congestion beyond this point pre-

sumably results in the compression of available space within the kidney, particularly the tubular lumina, eventually interfering with kidney function.

The findings in Case 9 appear to justify a simple mechanical explanation of this sort. There was no change in blood pressure, no dehydration and no salt loss. This case, in addition, showed certain classic clinical features of uremia. The uremic frost was marked. The terminal stupor progressing to coma resembled that seen in organic kidney disease.

10. *Intravenous and Transfusion Reactions:*

Case 10. A 46 year old man was admitted to Boston City Hospital, for treatment of an indolent ulcer of the left leg believed to be due to Buerger's disease. Previous admissions had revealed no findings of significance except those referable to partial occlusion of the arteries of both legs. The blood pressure had always remained about 130 mm. Hg systolic and 80 mm. diastolic. The renal function was normal. Physical examination on this admission revealed no new signs. The patient was treated by means of 200 c.c. of 5 per cent saline given three times weekly. He did well and after several weeks the ulcer began to heal.

A month after admission, following by one hour an injection of 5 per cent saline intravenously, the patient had a severe chill and began to vomit. The next morning jaundice was noticed. The pulse increased to 120 while the temperature rose to 103° F. The jaundice increased, the face and extremities became puffy, the conjunctivae chemotic, and hemorrhagic manifestations appeared. Significant changes in the laboratory data are tabulated in table 5. Unfortunately the presence or

TABLE V

	Blood Pressure		N.P.N.	Sp. Gr. Urines	Urinary Volume	Icterus Index
	Systolic	Diastolic				
Before reaction	130	80	25 mg. %	1.020	Normal	4
After reaction (only extremes tabulated)	140	80	155 mg. %	1.028	Progressive diminution to complete anuria	100

absence of hemoglobinuria was not ascertained. The liver was slightly palpable. Repeated blood cultures showed no growth. The patient continued on a progressively downhill course, developed anuria, lapsed into coma and died five days after the onset of the reaction. The postmortem examination revealed a normal sized liver with scattered areas of necrosis, atherosclerosis of the peripheral arteries and terminal bronchopneumonia. Blood cultures were negative. The combined weight of the kidneys was 540 gm. The cortex was 1.2 cm. wide. Microscopically there was no evidence of vascular or glomerular involvement. The convoluted and collecting tubules contained granular material. The tubular epithelium was somewhat flattened.

This bizarre clinical picture resembles closely that reported in other instances as following certain transfusions.[74, 75] Hench [76] reported a quite similar reaction following the intravenous injection of typhoid vaccine. This naturally raises the question as to whether some common mechanism underlies these seemingly isolated types of reactions.

An analysis of the above case shows that salt loss, dehydration and hypotension were not operative here. Liver damage was not sufficient to be a factor. Excessive protein catabolism alone could scarcely be responsible for a rise of blood non-protein nitrogen to 155 mg. per cent. The kidneys showed evidence of tubular damage and much debris blocking the tubular lumina. It thus seems that the local renal factor was most important here.

This appears to agree with the results secured by DeGowin et al.[52] in explaining a similar syndrome due to blood transfusion reactions. These workers showed that in acid urine, the excretion of hemoglobin caused obstruction of the tubular lumina with masses of pigment derived from hemoglobin. Unfortunately, in our case, no search for hemoglobinuria was made. The hemolysis of blood caused by the injection of any deleterious substance would allow us to explain these reactions on a mechanism similar to the one proposed by DeGowin et al.[52] Further study is obviously needed.

11. *Weil's Disease:*

*Case 11.** A 38 year old man was admitted to the Boston City Hospital severely prostrated and jaundiced. For one week, weakness, muscle pains, prostration, chills, vomiting and progressive jaundice had been noted. Physical examination revealed severe icterus, moist râles in the chest, hemorrhagic herpes of the lips, mucous membrane bleeding, a distended abdomen and tender thigh muscles. Blood pressure was 120 mm. Hg systolic and 50 mm. diastolic.

The urine was highly concentrated, and contained albumin and many granular casts. There was a leukocytosis of 28,700. The non-protein nitrogen of the blood was 200 mg. per cent, the sugar 55 mg., the cholesterol 90 mg. and the total protein 4.4 gm. per 100 c.c. The blood phosphorus was 13.6 mg. and the calcium 10 mg. per cent. The patient lapsed into coma and died 16 hours after admission.

The postmortem findings were typical of Weil's disease. The combined weight of the kidneys was 530 gm. The cortex was 8 mm. wide. Microscopically, interstitial infiltration of a multicellular type was noted, for the most part in the medulla. Some of the tubules were dilated and their epithelium showed evidence of regeneration. In certain tubules granular debris was present. In about a fourth of the convoluted tubules there was swelling of the epithelial cells with narrowing of the lumina. Spirochetes were found in the convoluted tubules.

Azotemia is constantly present in the second stage of severe cases of Weil's disease.[77] In mild cases it may be absent. It is well known that tubular damage and blocking of the renal tubules by granular debris are commonly present in this disease. In view of the close similarity between Weil's disease and yellow fever, one must not overlook the possibility of liver damage contributing to the azotemia. This has been shown to be so for yellow fever.[88] Dehydration is in addition common. The tubular changes must be considered reversible, since the patients who recover regain entirely normal renal function.

12. *Addison's Disease:*

Case 12. A 12 year old girl was admitted to the Evans Memorial Hospital in a moribund state. For six months she had had progressive fatigue, weakness, anorexia,

* This case was previously reported in detail.[77]

vomiting, weight loss, cramp-like pains in the abdomen and legs, and bronzing of the skin. Physical examination revealed prostration, emaciation, bronzed and pigmented skin and mucous membranes. The pulse was 108; the blood pressure was 74 mm. Hg systolic and 44 mm. diastolic.

The blood sugar was 68 mg. per cent and the non-protein nitrogen 120 mg.

The postmortem findings were consistent with the clinical diagnosis of Addison's disease, both adrenals showing marked atrophy. There was no evidence of tuberculosis. The combined weight of the kidneys was 225 grams; they showed no gross changes. Microscopically there was no evidence of vascular or of glomerular disease. There were slight engorgement and edema with some lymphatic infiltration. About one-third of the tubules showed swelling of the epithelium, with eosinophilic cells and pyknotic nuclei. Some of the lumina were filled with granular debris.

Marshal and Davis [78] first pointed out the occurrence of a rise in the non-protein nitrogen of the blood following adrenalectomy. This was also found fairly consistently by Rowntree.[79] Later Loeb and his coworkers [80, 56] demonstrated the urinary loss of sodium associated with adrenal insufficiency. This loss of sodium, chiefly as chloride, was then confirmed by other workers. It was suggested that the adrenals probably exert a regulating influence on body sodium.[56]

Other factors besides this loss of sodium influence the elimination of non-protein nitrogen from the blood in Addison's disease. The loss of sodium chloride is associated with varying degrees of dehydration. Also the typical asthenia of this disease is associated with a progressive lowering of the blood pressure. As already discussed in this paper, Loeb et al.[56] have suggested that the lack of the adrenal cortical substance acts specifically to cause urea retention in the blood stream.

In view of this patient's youth and lack of history of renal disease it was felt that this case was of particular interest here. This viewpoint was justified by the minimal degree of renal damage seen at autopsy. All changes are confined to the tubules, only about a third of which were involved and those only to a degree which would generally be termed moderate.

13. *Pneumonia:*

Case 13. A 45 year old negro was admitted to the Boston City Hospital, complaining of cough and dyspnea. He had been well until five days before when he had a chill, and subsequently began to cough and raise small amounts of whitish sputum which was sometimes blood-streaked. There was no chest pain. He had been perspiring profusely during the past four days. There was no history of previous renal disease.

On physical examination of the chest signs of consolidation were found in the upper portion of the right lung and in the base of the left lung. The blood pressure was 110 mm. Hg systolic and 60 mm. diastolic. The temperature was 103° F., pulse 140 and respirations 50.

The urine had a specific gravity of 1.014, contained albumin but no casts or pus cells. The hemoglobin was 86 per cent, the leukocyte count 10,800. A type V pneumococcus was obtained from the sputum and blood. The non-protein nitrogen was 70 mg. per cent.

The patient's condition grew rapidly worse and he died two days after admission.

The autopsy revealed the presence of lobar pneumonia of the right upper and left lower lobes with extension to all remaining lobes. The combined weight of the kidneys was 360 grams. The width of the cortex was 0.5 cm. Microscopic studies showed minor degrees of tubular damage. The glomeruli appeared normal. Some of the tubular lumina contained granular debris.

In view of the discordant results of earlier investigations, Farr and Abernathy [81] carefully studied the renal function in 28 cases of pneumonia. The urea clearance test indicated an actual increase in this type of renal function in the pre-critical stage of the disease particularly in the younger age group (i.e. up to an age of 40). They concluded that in the pre-critical phase of pneumonia renal function may be elevated, unchanged, or slightly impaired. In general they noted that the level of renal activity was inversely proportionate to the age of the patient.

Of particular interest are two cases in their series which exhibited high blood urea nitrogen values on admission, with low urea clearance, both of which returned to normal during the next few days. It was felt that these patients were probably dehydrated and that extrarenal factors played a dominant rôle in the production of these changes.

The occurrence of hypochloremia during the course of lobar pneumonia has been recognized for some years.[82] Several workers have found the sodium to be diminished as well.[85] Low total base values have likewise been reported.[85] More recently, Atchley [83] has brought forth the conception that a shock-like state exists in pneumonia, with accompanying dehydration, and hemoconcentration.[84]

To go one step further, it has been noted that, with various infectious diseases including pneumonia, it is not unusual to find hemorrhagic necrosis of the adrenals post mortem.[57]

In summary, then, increased protein catabolism, dehydration, electrolyte disturbance, lowered blood pressure and toxic damage to the adrenals and kidneys are significant factors in producing azotemia in pneumonia.

Case 13 is illustrative of azotemia in pneumonia. It was not well enough studied to permit critical evaluation of the factors responsible. At autopsy the evidence of renal tubular damage was striking.

14. *Allergy.* Rackemann, Longcope and Peters [47] in 1916 confirmed the fact that in serum disease there was often a marked but transient retention of chlorides and of water, associated frequently with albuminuria, cylindruria, and sometimes with impaired phenolsulphonephthalein excretion. The kidneys in these cases showed an impaired ability to eliminate chlorides and loss of power to concentrate urine. The following year Longcope and Rackemann [86] reported two interesting cases of azotemia associated with attacks of urticaria. In each case with the onset of the acute allergic state, albumin and casts appeared in the urine, the phenolsulphonephthalein excretion diminished and the blood non-protein nitrogen rose (in one instance the blood urea nitrogen reached a level of 290 mg. per cent). Plasma chloride values were low. Even with so high a degree of nitrogen reten-

tion as that mentioned, the patients recovered rapidly and completely. The cases were not studied from the viewpoint of this paper and therefore the exact mechanism responsible is not clear. There seems little doubt that allergic states can produce an azotemia of extrarenal origin.

15. *Diabetes Mellitus.* Many clinicians and investigators are aware of the frequent association of diabetic coma and azotemia.[87] This is often erroneously attributed to kidney disease.

Peters et al.,[88] in a study of the total acid-base equilibrium in diabetics, called attention to (1) the loss of fluid because of glycosuria, polyuria, base excretion and vomiting; (2) loss of base bound to ketones which are thus excreted in the urine; and (3) the availability of base released from chloride for ketone neutralization. It was pointed out that the result is a state of dehydration and salt depletion as well as acidosis. Atchley and Benedict [89] arrived at similar conclusions. The dehydration causes a decrease in blood volume with consequent decrease in blood pressure and increase in the percentage of blood proteins.

McCance and Lawrence [87] reviewed the proposed mechanisms supposedly explaining the production of extrarenal azotemia in diabetic coma and concluded that no proposed mechanisms including dehydration, failing circulation, low blood pressure, excessive protein catabolism, action of insulin, ketosis and salt depletion could be invariably and wholly responsible for the extreme and consistent degrees of nitrogen retention which occurred in some of their cases. These authors believe that another mechanism must be present. They point to the similar occurrence of nitrogen retention in Addison's disease and conclude that the causes may be similar, that is a deficiency in fixed base which may be brought about not merely by acidosis and diuresis but possibly by a partial failure of the suprarenal cortex.

16. *Shock.* Moon [29] has been able to show that the advanced stages of shock are invariably associated with an increased blood non-protein nitrogen. Drop in blood pressure and loss of circulating blood volume seem to be the chief factors concerned. Moon [90] lists a large group of diseases in which severe shock (and therefore azotemia) occurs. Blood is lost by being shunted into stagnant depots. Also, changes in capillary permeability cause loss of fluid and electrolytes into interstitial tissues.

17. *Acute Pancreatitis.* DeTakats and Mackenzie [91] recorded a case of pancreatitis with azotemia. They expressed the view that it would commonly be found if examinations of the blood chemistry were routinely performed in this disease. The same mechanisms used to explain azotemia in shock probably apply here.

18. *Diarrheal Diseases.* As one would expect, fluid and salt loss are the chief initiating factors.[92] Not to be overlooked are fever, starvation, and infection; all of these can increase protein catabolism. With severe dehydration the blood pressure falls. Toxic damage to kidney tubules may occur.

19. *Heat Cramps.* Talbott [93] has demonstrated that in heat cramps the

blood sodium and chloride are diminished. Hemoconcentration and azotemia are constant features. The disease is initiated by excessive loss of sodium chloride in the sweat. Here is an interesting example of dehydration due to sodium loss. In most cases these persons continued to drink water which is, however, of no avail until the sodium chloride loss is replaced.

20. *Drug Intoxication.* A few drugs seem to affect nitrogen metabolism. Of these, the iodides are probably the most outstanding. Grabfield and his co-workers [49] showed that the continued use of potassium and sodium iodides may cause an increase in the output of nitrogen in the urine. Potassium iodide particularly may cause an increase in the blood nonprotein nitrogen, amounting sometimes to 30 per cent of normal values and occasionally reaching abnormal figures. These results were attributed chiefly to an increased rate of protein catabolism. The possible deleterious effect of potassium on kidney function must not be forgotten.

Of the chemicals and poisons which may affect kidney function indirectly, phosphorus and chloroform [37] are the most common. If the kidneys are not directly involved, azotemia may result because of liver cell destruction, and consequent loss of the ability of the liver to deaminize amino acids. An increased rate of protein catabolism may be present. More often than not, actual renal insufficiency supervenes, and the blood urea nitrogen increases in relation to the increasing urea threshold in the kidney.

21. *Burns.* The relation of superficial burns to azotemia is important. In 1923 Underhill and his co-workers [94] demonstrated that many of the constitutional effects of extensive burns were due to the presence of marked hemoconcentration. This was borne out by the fact that improvement followed in most instances when the normal blood volume was restored.

At about the same time Robertson and Boyd [95] stressed the factors of primary shock occurring in those cases which terminated fatally within the first 24 hours, and toxic shock which resulted in a later death. The latter very likely is what is now recognized as the syndrome of hemoconcentration.[84]

Later Davidson [96] in studying the sodium chloride metabolism of patients suffering from burns found a significant lowering of the blood chlorides. In general, the disturbance of chloride metabolism was proportionate to the amount of devitalized tissue. Davidson also believed that an increased rate of protein catabolism accompanied lesions of this sort.

Recent investigators have focused their attention sharply on sodium metabolism and the adrenal glands.[57] As evidence accumulates it seems more and more probable that adrenal hormonal regulation with control of sodium metabolism and restriction of urea excretion may be a basic factor in conditions of this type. The presence of pathological changes in the adrenals noted at postmortem examinations of patients who have died as a result of severe burns would appear to give added weight to this point of view.[57]

In summary then the lowered blood pressure, increased protein catabolism, hyponatremia and hypochloremia, dehydration and toxic damage to the adrenals are chiefly responsible for the azotemia found in burns.

Clinical Picture of Extrarenal Uremia

The clinical picture of the classical type of uremia due to organic kidney disease has been well reviewed by Fishberg [97] and more recently by Harrison and Morton.[98] Fishberg [97] defines uremia as "a complex autointoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents, largely, it would seem, end-products of protein catabolism." He further remarks "no group of symptoms is to be considered as uremic in nature unless it occurs in the presence of abnormally high non-protein nitrogen in the blood."

The mechanisms described in this paper can undoubtedly cause the retention of other substances besides the nitrogenous waste products. This would fulfill the requirements of the above definitions. Harrison and Morton [98] state that the syndrome of prerenal azotemia resembles true uremia in both its chemical and clinical aspects.

True uremia will always be found a concomitant part of the clinical picture of organic renal failure. Since few renal diseases are fulminating, the symptoms are often present for weeks or months.

Extrarenal uremia, on the other hand, must of necessity be superimposed on the clinical features of many widely varied and entirely unrelated diseases. Further, the diseases which cause this type of uremia are usually acute and fulminating, their duration being one of days. For this reason the clinical manifestations of chronic uremia (i.e. yellowish pallor of the skin, pericarditis, uremic colitis with diarrhea, severe anemia, extreme dryness of the skin, uremic eruptions and emaciation) are but rarely seen. The chief features of extrarenal uremia seem to be fatigue and drowsiness, progressing into stupor and coma within a period of a day or longer. Case 9 in our series showed the classical deposit of uremic crystals on the skin. Case 8 presented muscular twitchings. What should be particularly emphasized is that we lack a careful chemical analysis of cases falling into this group and that such a study is needed in order to define more clearly the clinical picture of extrarenal uremia. Whether the non-excretory functions of the kidneys are affected in this syndrome to a degree sufficient to be clinically detectable is at present not known. Snapper [99] believes them important in explaining uremia.

Anuria

One hears only too frequently such expressions as "the patient's kidneys have closed down, the patient has developed reflex anuria, etc." Even more unfortunate is the fact that many physicians treat all oliguric and anuric patients in a routine fashion without attempting to evaluate properly and specifically treat the factors responsible for the diminished or absent kidney

function. It is evident that the problem of anuria is closely linked with the problem of azotemia. Essentially, anuria may be looked upon as an exaggerated degree of oliguria. Therefore, a discussion of the mechanisms involved in the production of anuria will clarify both subjects.

The most satisfactory working classification of the anurias is that which divides them into one of the following categories: (1) Prerenal, (2) Renal and (3) Postrenal.[100]

Prerenal. In prerenal anuria the causative factors lie outside of the kidneys and genito-urinary tract. It is immediately evident that this type of anuria represents but a severe degree of several of the mechanisms previously discussed; that a drop in blood pressure sufficient to nullify the intraglomerular pressure will produce anuria; and that severe degrees of dehydration and sodium chloride deficiency may also produce anuria.

The existence of reflex anurias has been disputed. That splanchnic stimulation can diminish urinary function is well established. The usual reflex anuria means complete cessation of function in one kidney following some catastrophe to the other.[100] It has been suggested also that stimuli to the renal splanchnics may arise from nerve insults outside of the renal system causing an inhibition of function of all renal tissue. Such a mechanism if it exists must be included with the prerenal group of anurias. It would explain anuria following such widely varied events as immersion in cold water, hysteria, and operations on organs distant to the genito-urinary tract. Of interest is Cubitt's statement [3] that most case reports in which reflex anuria has been postulated do not contain blood pressure measurements nor facts relating to other mechanisms controlling renal function.

Renal Anuria. Renal anuria refers to factors operating primarily within the kidney. In addition to diffuse inflammatory lesions, chemical damage, neoplastic invasion, mechanical destruction, removal, congenital defects and degenerative changes, one must also include edema of the kidneys due to venous congestion or tubular occlusion due to nephrotic changes. These latter two have already been discussed under local conditions causing azotemia. When of severe degree they can readily produce anuria.

Postrenal. Postrenal anuria refers to the type due to mechanical factors causing obstruction to the outflow of urine. These are either bilateral or unilateral and in the latter instance may be associated with reflex anuria or subnormal renal function of the opposite kidney.[101] The majority of the cases falling in this category are due to ureteral calculi or strictures or to urethral obstruction. Where the possibility of this type of anuria exists the patient should be studied intensively by urological methods.[101]

Discussion. The foregoing classification allows a more rational approach to the problem of anuria. It is evident that an understanding of the mechanisms involved clarifies the study of any particular case. By discarding obscure and complicated classification dependent primarily on the relationship between anuria and a wide and varied number of systemic con-

ditions, one's attention is necessarily focused on the few fundamental mechanisms involved in the production of anuria.

The treatment of anuria will necessarily depend on the primary disturbance by which it is produced. If obstructive lesions of the genitourinary tract and intrinsic renal disease are ruled out, the remaining mechanisms which produce anuria are the same as the mechanisms discussed under the production of prerenal and functional azotemia, and should be treated in a similar fashion.

Methods of Differentiating Azotemias

Since the mechanisms producing azotemia are numerous, it is evident that a somewhat elaborate diagnostic study of cases of unexplained azotemia will be necessary. The first consideration in explaining any azotemia should be the investigation of whether true organic renal disease, or the mechanisms discussed in this paper are responsible.

Renal lesions which produce true uremia, as a rule, cause changes in the urine distinct from those seen in functional azotemia. Fishberg comments on this fact.[97] In true uremia the specific gravity is usually fixed at a low level, often 1.010, and only rarely as high as 1.015. In sharp contrast is the specific gravity of the highly concentrated urine of functional azotemia which may range as high as 1.040. Exceptions to this are some of the cases with severe tubular damage as a complication to the extrarenal factors. Here the specific gravity may be lower. These changes, however, develop far more rapidly than in the usual organic renal diseases.

The volume of urine is not so important since it may be diminished in both types. It is evident that the finding of albumin, casts and cells in sediment is often of little differential value. The general clinical picture will probably be the most important aid in determining whether or not organic renal disease is present.

If it is believed that azotemia is of the type discussed in this paper an effort should be made to determine which of the basic mechanisms is present. This may entail detailed laboratory study of the case, but since functional azotemia is frequently reversible, a knowledge of the causative mechanisms will often point to therapy which may prove life saving.

From this point of view the minimum information needed would include: The systemic arterial blood pressure; 24 hour fluid intake and urinary output; measurement of fluid lost by extrarenal channels; urinary specific gravity; presence or absence of ketonuria; blood sodium; blood chloride; carbon dioxide combining power; total blood protein; erythrocyte count; hemoglobin; hematocrit value; and blood non-protein and urea nitrogen. If the patient has liver disease a nitrogen partition of the blood should be performed including the amino-acid nitrogen. In the case of congestive heart failure or obstruction of the inferior vena cava, the venous pressure obtained in the femoral vein would be of value. The factor of protein cata-

bolism could only be resolved by complete nitrogen studies such as would be impractical for routine clinical use.

With dehydration various constituents of the blood increase in addition to the non-protein nitrogen. Since the blood urea content does not increase in proportion to the loss of fluid, it is evident that the degree of dehydration cannot be determined from the level of the total non-protein nitrogen or any of its constituents. A much better criterion of the degree of dehydration is the increase of total blood protein, erythrocyte count, hemoglobin or hematocrit value. The simplest to use, and probably the most accurate, is the hematocrit value (volume per cent of erythrocytes per 100 c.c. of blood). A single reading (unless well over normal) is not nearly so valuable as serial studies. By this means, the progression or regression of the dehydration can be quantitatively determined. If there is a possibility of the patient having an anemia or blood loss the total blood proteins could be substituted with advantage.

Blood sodium and blood chlorides should be determined separately, if possible. Few laboratories are equipped to perform routine sodium determinations at present. As previously pointed out, chloride and sodium levels do not always parallel each other. When only blood chlorides are determined, this fact should be kept in mind.

Indirectly, the sodium level can be roughly surmised in many cases from a comparison of the blood chloride level and the carbon dioxide combining power. If the carbon dioxide combining power is high (alkalosis) and the blood chloride level is low, then the sodium level is probably near normal. Conversely a low carbon dioxide combining power (acidosis) with normal or slightly low blood chloride level speaks for the presence of an hyponatremia. This knowledge aids greatly in treating the disturbed electrolyte and fluid balance.

Treatment

Rational therapy in instances of this syndrome is necessarily dependent on the determination of the fundamental mechanisms responsible for its production. Due consideration must also be given to the underlying disease process, specific therapy of which may occasionally be available.

In many cases the factors of dehydration and salt deficiency are coincident. The fluid needs of the patient can be roughly calculated from the following program suggested by Coller and Maddock.[26] The fluid intake should be sufficient to (1) furnish 1500 c.c. of urine daily, (2) replace abnormal fluid losses such as vomitus, drainage from fistulae, diarrhea, etc., and (3) replace water of evaporization from skin and lungs which amounts to 1000 to 1500 c.c. daily in uncomplicated cases. With increased heat production, fever, high basal metabolic rate or sweating in hot and humid environments, this loss may amount to 1500 to 3000 c.c. of fluid per day.

An initial infusion amounting to 6 per cent of the total body weight may safely be given at the beginning of serious dehydration.[26] Normal saline

is the fluid indicated in most cases. If the patient should be dehydrated, but not suffering from salt loss, 5 per cent glucose in distilled water could be utilized. In severe alkalosis (where the blood sodium is near normal and the chlorides markedly depressed) normal saline may at times fail to correct the electrolyte disturbance. Under such circumstances fluid should be given as isotonic glucose in distilled water and the chlorides supplied by means of ammonium chloride, calcium chloride or even hydrochloric acid. In severe acidosis, where the hyponatremia exceeds the hypochloremia, part of the sodium deficit can be supplied as sodium lactate solution.[102] Where the salt loss greatly exceeds the fluid loss (i.e. in Addison's disease, toxic adrenalitis) it may be necessary to give sodium chloride in addition to that present in physiologic saline. Large oral doses or injection of hypertonic salt solutions is then indicated. Root[103] calls attention to the fact that anurias which fail to respond to injections of normal saline may do so after the use of hypertonic salt solution.

Fluids may be given orally, intravenously or hypodermically. If the latter method is used, the isotonicity of blood should not be exceeded. It is impossible to give sufficient fluid by rectal instillation alone, although this method can be used to supplement other procedures. Often overlooked is the possibility of giving large volumes of fluid by means of a Levene tube passed into the duodenum and left in place.[104] Some authors believe this to be a better method than the intravenous route.[100] It has the great advantage that nutrient foods can be added to the infused fluid.

In the event of a high non-protein nitrogen due to liver disease the intake of carbohydrates should be increased and the fat and protein diminished. At least 400 grams of carbohydrate are needed daily.

If starvation has been present the protein requirements should be satisfactorily met. Glucose therapy is indicated when acidosis is present.

Where high venous pressure is a factor, specific cardiac therapy and possibly venesection would be of value.

The maintenance of a systolic blood pressure greater than 70 mm. of Hg is desired. Blood pressures below this level are usually associated with collapse and shock which must be vigorously treated. The restoration of the normal circulating blood volume will entail intravenous injections of saline, glucose or blood. The patient should be put in "shock position," heat artificially supplied, and oxygen therapy instituted. Strychnine, caffeine, coramine, cardiazol, ephedrine and benzedrine are among the drugs which may be of value. Weiss and Wilkins[105] have recently discussed this aspect of the subject at length.

Where adrenal damage is suspected, and certainly in Addison's disease, the use of adrenal cortical hormone should not be overlooked.[106]

In spite of these medical procedures, patients may at times show a progressive increase in azotemia and oliguria, terminating in anuria. This is often due to tubular damage, edema of the kidney or possibly to reflex anuria. There seem to be two surgical procedures which at times may be

valuable. Some striking cures have been reported. The chief obstacle to their use seems to be the lack of any clear cut criteria as to when they are indicated. Few physicians have had any experience with them.

The simplest, and to be tried first, is the sectioning or blocking of the renal sympathetics. This can be done by paravertebral injection of a local anesthetic.[101] Cubitt [3] has reported excellent results in reflex anuria by the simple procedure of spinal anesthesia. Milliken and Karr [51] favor the use of periarterial sympathectomy.

Where swelling of the kidneys exists bilateral decapsulation may be life saving. Dunn and Dunn [107] have reviewed this subject and offer a remarkable example of such a cure. Such radical procedures should be attempted only under the guidance of an experienced internist and genito-urinary surgeon.

Besides replacement and supportive therapy, every effort should be made to prevent undue loss of fluid and electrolytes. This may mean operation in the case of pyloric obstruction, coagulant therapy in the case of superficial burns, change of environment in the case of excess sweating, repair of fistulae, treatment of diabetes mellitus to relieve polyuria, etc. Such treatment of the underlying disease may prevent the factors causing azotemia from continuing to act. Therapy to relieve azotemia should never be considered to the neglect of such treatment of the underlying disease.

Discussion

To many physicians an elevated blood non-protein nitrogen means kidney disease. It has been our experience on several occasions to meet surgeons who refused to operate on persons with an obstructed pylorus or peritonitis because of an azotemia and the presence of albumin and casts in the urine. These patients were diagnosed as having "kidney disease" or "nephritis" and therefore considered poor operative risks. Such a view is of course not tenable. In routine clinical practice, an azotemia is much more commonly due to the mechanisms discussed in this paper than to organic renal disease. At present, non-protein nitrogen determinations are rarely performed except for persons suspected of having renal disease. Routine and serial blood chemical studies for all the diseases mentioned previously would undoubtedly reveal a striking number of instances of azotemia.

Another common misconception is that the level of the blood non-protein nitrogen in extrarenal azotemia rarely increases to a degree comparable with that seen in organic renal disease. Quite the opposite is true. Values of 100 or even 200 mg. per cent are common. Not only may such high figures be observed, but frequently they develop within a few days and may disappear as rapidly, if the patient's underlying disease is amenable to treatment. Fishberg [97] mentions a patient with prerenal azotemia in which the blood non-protein nitrogen increased to 400 mg. per cent in three days and diminished in an equally striking fashion following therapy.

The ubiquity of this syndrome should be kept in mind. There are few specialties in which it will not at some time be encountered.

It is hoped that this presentation will aid in clarifying the clinical concept of extrarenal azotemia, though the problem still presents numerous questions to be solved. It is a subject which deserves more attention from the medical profession and which should not be neglected in presenting the problem of renal disease to medical students.

Conclusions

The syndrome of extrarenal azotemia is present in a wide variety of unrelated and often common diseases. The basic mechanisms producing this syndrome have been analyzed and include: (1) Fall in blood pressure; (2) hypochloremia and hyponatremia; (3) dehydration; (4) increased protein catabolism; (5) loss of deaminizing power of the liver; and (6) local renal factors. Reasons are given why cases with tubular damage or edema of the kidney should be included in this syndrome. These mechanisms are interdependent and interrelated and present in varying combinations in different diseases. The relation of the anurias to this syndrome is discussed. Diseases associated with azotemia have been analyzed with this concept in mind. Methods for evaluating the syndrome and consequent procedures for logical treatment have been presented.

Note: Since the preparation of this paper several interesting and pertinent contributions have appeared in the literature. In continuing the search for a toxic substance elaborated in instances of high intestinal obstruction, Scudder, Zwemer and Truszkowski (Surgery, 1937, i, 74) demonstrated experimentally a resulting rise in blood potassium which attained definite lethal proportions. This suggests the need for further study of the potassium factor in extrarenal uremia. Gömöri (Acta med. Scandinav., 1937, xcii, 497, 503, 515; 1937, xciii, 42) has produced considerably more evidence to substantiate his original views on extrarenal azotemia. Wohl and his co-workers (Jr. Lab. and Clin. Med., 1938, xxiii, 450) have brought forth experimental and clinical data indicating that adrenal damage is often associated with instances of uremia of the extrarenal type. Indeed, as our knowledge of this syndrome increases, the importance of the adrenals becomes more and more impressive. In an exhaustive paper on acute renal pathology, Bell (Am. Jr. Path., 1937, xiii, 497) has included findings in certain cases in which extrarenal factors had been present. These consisted chiefly of distortion of the convoluted tubules with minor degenerative changes in their lining cells. The influence of these minor pathologic changes on renal function are discussed.

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CASE REPORTS

LARGE PERICARDIAL EFFUSION COMPLICATING ACUTE CORONARY THROMBOSIS *

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The clinical features of the pericarditis found during the course of some cases of acute coronary artery thrombosis have been recently reviewed by Blumer [1] who rejuvenated the term *pericarditis epistenocardica* first applied to this condition in 1910 by Sternberg.[2] In 1872 Baumler [3] gave the first clinical picture of *pericarditis epistenocardica,* though he was not aware of the relation of the condition he described to acute coronary artery thrombosis and in fact dubbed the pericarditis "idiopathic." He called attention to the absence of pericardial effusion in his cases. White [4] comments on the infrequency of pericardial effusion following coronary thrombosis and avers it is of no clinical significance. Levy [5] states he has never seen effusion in detectable amount associated with coronary thrombosis but in a footnote relates that Herrick has seen one case. Levine [6] in his recent monograph on heart disease says "Only on very rare occasions is pericardial effusion associated with this type of pericarditis" but does not cite a case in his own experience. Schwartz,[7] in 1934, was the first to record the clinical detection of pericardial effusion following acute coronary occlusion, his case being that of a man of 50 years who improved after pericardial paracentesis and eventually recovered. Master and Jaffe [8] reported the following year two cases, both of whom recovered without pericardial paracentesis. These authors believe that pericardial effusion of similar origin must be less rare than the clinical reports published make it appear. The present case is of interest because the effusion was of enough volume to make paracentesis an essential therapeutic procedure and also because following recovery a carcinoma of the cecum was successfully removed.

Case Report

Mr. E. D., a white male of 64 years, with previous good health except for constipation, slight anemia, occasional dyspnea on climbing stairs, and one attack of angina of effort, was stricken on the night of March 6, 1935, with heavy substernal oppressive pain which radiated to the left arm and lasted several hours, relief being obtained only after 30 mg. morphine sulfate were given hypodermically by his physician. Weakness and sweating followed the pain. He was kept at rest, but three days later had a similar attack severe enough to again require 30 mg. of morphine sulfate for relief. The blood pressure was 95 mm. of Hg systolic and 60 diastolic, the pulse weak and the skin moist and cool. The temperature rose during the next few days to 100° F. and a pericardial friction rub was heard on the seventh day, by which time the diagnosis of acute coronary artery thrombosis seemed well established although an electrocardiogram and leukocyte count were lacking. The low grade

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fever terminated on the twelfth day, after which time the patient was fairly comfortable until the seventeenth day when the temperature rose to 101° F. with the advent of mild substernal pain. He then became weaker and complained of pains through the left chest, so by the end of the third week of his illness, on the occasion of my initial visit, he appeared distressingly ill, was mildly cyanosed and orthopneic. The temperature was 102° F., the pulse soft, rate 124, with sinus arrhythmia, and the blood pressure was 98 systolic and 70 diastolic. Increased venous pressure was indicated by venous pulsation in the neck veins when in the erect position, but no direct measurement was made. The left border of cardiac dullness by percussion extended to the anterior axillary line at the sixth interspace, and the right border was 1 cm. beyond the right sternal margin. The apex beat was not located and the heart sounds were somewhat indistinct. There was dullness at the left lung base, with exaggeration of breath sounds, and moist râles at both bases. The liver edge was 3 cm. below the right costal border and there was moderate edema of the ankles.

The diagnosis of pericardial effusion following coronary artery thrombosis was suggested. An *electrocardiogram* (3–28–25) revealed slight depression of the RS-T segments in Lead I, with T_1 slightly positive, while conversely in Lead III there were slightly elevated and coved RS-T segments and inverted T-waves. T_2 was inverted. Q_2 and Q_3 were prominent. In Lead IV there was definite elevation of the RS-T segment, and the T-waves did not dip below the isoelectric level. These changes were considered fairly typical of a late Q_3T_3 pattern (this record was made three weeks after the initial episode) indicating infarction, probably in the posterior basal portion of the left ventricle. (Sections of this and subsequent electrocardiograms are depicted in figure 1.)

The hemogram showed red blood cells 3,300,000, white blood cells 9,650, hemoglobin 60 per cent. Neutrophiles were 83 per cent, lymphocytes 14 per cent, mononuclears 3 per cent. The blood Kahn and Mueller tests were negative. There were 30 mg. non-protein nitrogen and 1.5 mg. creatinine per 100 c.c. of blood. A urinalysis was normal.

Radiographic examination (figure 2-A) showed marked general enlargement of the "cardiac" shadow, even after allowing for distortion due to the semi-recumbent position of the patient and a target distance of only 30 inches; and the size and contour were considered suggestive of pericardial effusion. The lung fields showed the changes typical of congestive failure, but otherwise were negative.

Since it was felt that *Herz-tamponade* accounted for a good part of the patient's discomfort, a needle was inserted below the angle of the left scapula in the seventh interspace and 500 c.c. of amber thin fluid were withdrawn freely from the pericardial sac. The fluid showed 20–35 erythrocytes per field and only 1–3 leukocytes, with lymphocytes predominating on the stained smear. Cultures of the fluid were free from growth after seven days incubation. The improved "cardiac" contour two hours after the paracentesis is shown in figure 2-B, but part of the change was due to the more erect position of the patient and to the fact that this roentgen-ray was made at a distance of 5 feet. The measurements were: total transverse "cardiac" diameter 18.5 cm.; M.R. 9 cm.; M.L. 9.5 cm.; and internal diameter of chest 30 cm., giving a cardio-thoracic ratio of 60.1 per cent. An *electrocardiogram* made the following day (3–29–35) showed no significant change from the previous record.

Following the pericardial paracentesis the patient was greatly relieved, but owing to the evident congestive failure oxygen therapy, 50 per cent dextrose solutions intravenously and digitalis were employed. The rate of improvement was strikingly indicated when the patient remarked only 12 hours after the paracentesis that "he felt like a new man." The fever disappeared within 48 hours, and the following day a direct venous pressure reading was only 10 cm. of water. The heart gradually slowed, the blood pressure ranged from 100 systolic and 60 diastolic to 120 systolic

and 80 diastolic; and all signs of congestive failure cleared up at the end of a week. An *electrocardiogram* at this time (4–5–35) showed no essential change.

A small, slightly tender mass was discovered in the right lower quadrant of the abdomen and occult blood was found in the stools. Roentgen-ray examination of the colon revealed a "napkin ring" defect just above the ileocecal valve diagnosed as carcinoma of the cecum.

Improvement in the circulatory state was continuous. A teleoroentgenogram taken five weeks after the paracentesis, on May 11, 1935, showed further decrease in the "cardiac" size, the total transverse "cardiac" diameter measuring 16.5 cm.,

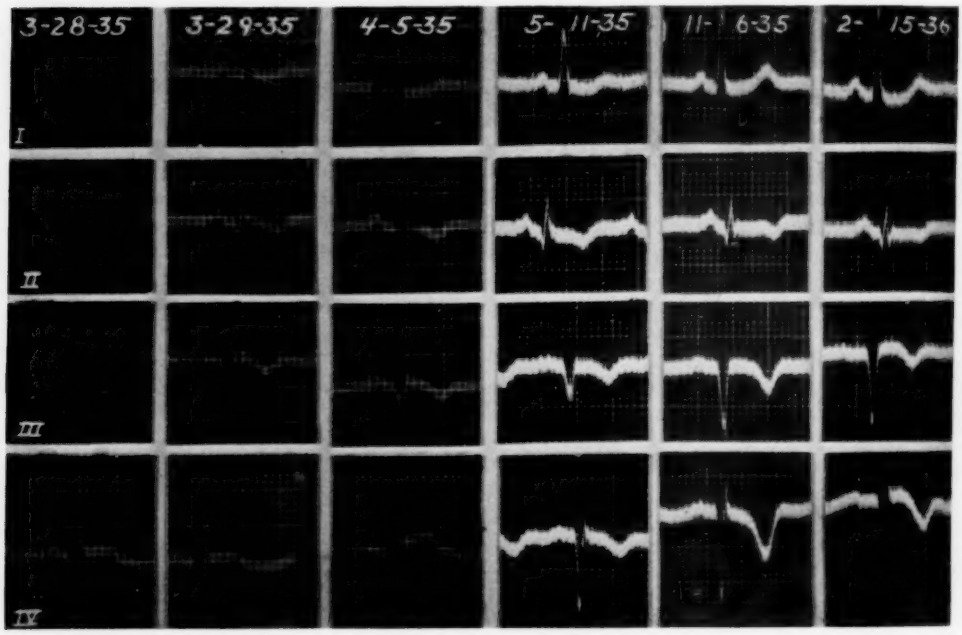

FIG. 1. Sections of serial electrocardiograms from patient with acute coronary occlusion complicated by pericardial effusion. The first curve taken three weeks after onset of attack, dated 3–28–35, shows a late Q_3T_3 pattern indicating infarction in the posterior basal portion of the left ventricle. No appreciable change is noted in the next curve taken the following day, in spite of fact that 500 c.c. of pericardial fluid had been removed. On 5–11–35 little change is noted in the electrocardiogram, although by this time all clinical signs of pericardial involvement had vanished, indicating the initial alterations were due to coronary occlusion rather than the complicating pericarditis. The curve of 11–6–35, showing some increase in voltage of the ventricular complexes, was taken just prior to resection of carcinoma of the cecum, while the last curve, taken 2–15–36, was after complete recovery from this operation (Lead IV, made with right arm electrode over fourth left interspace, the left leg electrode serving as indifferent electrode).

M.R. 6.5 cm., M.L. 10 cm., giving a cardio-thoracic ratio of 55 per cent. (Figure 3-A.) An *electrocardiogram* on the same date showed no significant change except that in Lead IV, the RS-T segments were no longer elevated and T_4 was now inverted. The patient was permitted gradually to be up and about, and, ten weeks after the onset of his attack, was able to go north where his strength and weight further improved, and roentgenologic reëxamination of the colon showed no demonstrable increase in the carcinoma. On his return south the following November there were no physical signs of heart disease, the blood pressure was 135 systolic and 80 diastolic, and the

heart appeared, on fluoroscopy, to be of normal size and contour. An *electrocardiogram* at this time showed improved voltage, T_1 frankly positive and deeper inversion of T_4.

As his recovery now seemed maximal, laparotomy was performed under spinal anesthesia, by Drs. J. W. Snyder and J. C. Turner. An adenocarcinoma of the cecum (grade 2) was found without malignant fixation of the parietes, or any glandular, pelvic shelf, or liver involvement demonstrable. Resection of the cecum and part of the ascending colon was followed by a Wetzel enterostomy proximal to an end to side anastomosis. A direct transfusion of 500 c.c. of blood successfully overcame the moderate shock produced. The post-operative course was noteworthy for its smoothness, there being an average amount of abdominal discomfort, but no circulatory symptoms other than occasional mild precordial pains. The enterostomy wound eventually closed, and the patient was up and about within a few weeks.

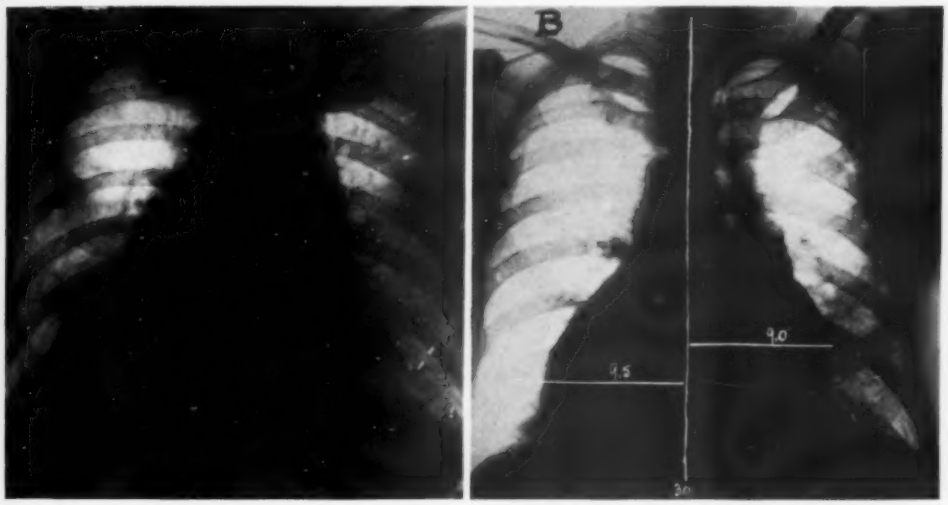

FIG. 2. Heart films made with portable equipment. A—taken 3-27-35, patient semi-recumbent, 30 inch distance, 3 weeks after acute coronary thrombosis, showing pericardial effusion. B—taken the following day, 2 hours after withdrawal of 500 c.c. of pericardial fluid, erect position, 5 ft. distance, transverse "cardiac" diameter 18.5 cm., internal chest diameter 30 cm., CT ratio 60 per cent.

A *teleoroentgenogram* on February 15, 1936, nearly a year after the acute episode (figure 3-B), disclosed a normal cardio-thoracic ratio of 49.3 per cent (total transverse cardiac diameter 14.8 cm., M.R. 5.3 cm., internal diameter of the chest 30 cm.). An electrocardiogram the same day showed little change from the previous record. The patient was last seen in April 1937 and felt very well except for moderate fatigue and occasional vertigo. He had gained 25 pounds (11.3 kg.) in weight, and was able to walk two miles a day without discomfort. The electrocardiogram at this time showed no further change.

IN REGARD TO ELECTROCARDIOGRAPHIC SIGNS OF PERICARDITIS

The changes in the electrocardiogram produced by *uncomplicated pericarditis*, with or without effusion, have been fully described recently by Schwab and Herrman.[9] Their conclusions, based on a review of the relevant literature

since the observations of Oppenheimer and Mann [10] in 1923, together with their own study of serial electrocardiograms in seven cases of pericardial disease, may be summed up as follows: The usual *early* alterations consist of low voltage of the ventricular complexes and elevation (never depression) of the RS-T segments in Leads I and II or all three conventional leads, although these changes may be lacking. The usual *late* alteration consists of inversion of the T-waves in the same leads, either following the regression of the RS-T segments to the isoelectric level, or appearing without preceding RS-T segment elevation. In the few instances where Lead IV was taken slight deviation in the RS-T segments and positive or biphasic T-waves were revealed. Although mimicking the electrocardiogram following acute coronary occlusion, pericardial disease is differentiated by the *absence* of reciprocal relationship in the RS-T

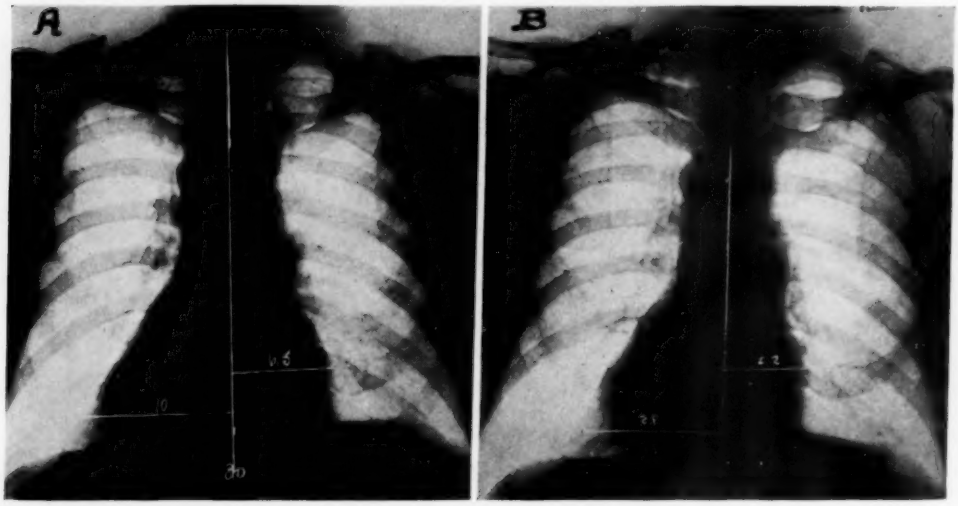

FIG. 3. Teleoroentgenograms of the same patient. A—taken 5 weeks after the paracentesis showing further decrease in "cardiac" size. Transverse "cardiac" diameter 16.5 cm., internal diameter of chest 30 cm., CT ratio 55 per cent. B—taken 7 months after A, and 3 months after resection of the colon. The transverse "cardiac" diameter is 14.8 cm., CT ratio 49.3 per cent or normal.

deviations and T-waves in Leads I and III, and by the *absence* of abnormal Q-waves. Serial electrocardiograms show that as the pericarditis heals the T-waves gradually become positive again.

The typical electrocardiographic pattern in *acute coronary occlusion complicated by pericarditis* is featured, according to a recent study made by Barnes,[11] by elevation or dome-shaped upward rounding of the RS-T segment in all three conventional leads, without the reciprocal depression of the RS-T segment either in Leads I or III characteristic of myocardial infarction. This change is followed by inversion of the T-wave in all conventional leads, or in some instances by a T-pattern typical of late coronary occlusion. Even early, however, the Q-pattern may be so typically developed that myocardial infarction, and its location, is indicated. In other words, this author holds that if acute coronary occlusion is attended by pericarditis, the characteristic early reciprocal deviation

in the RS-T segments in Lead I and III is overshadowed by the signs of pericarditis, i.e. elevation or dome-shaped upward rounding of the RS-T segments in all three leads, the only intact evidence of infarction in the early stage being the characteristic Q-pattern. There was no clinical evidence of pericardial effusion in the cases comprising Barnes' study.

In the case under discussion, proof that the first electrocardiographic changes were due to acute coronary occlusion (of 21 days' duration) rather than to the pericarditis, rests on the lack of electrocardiographic improvement following the disappearance of the clinical signs of pericarditis. Granting this, the retention of the characteristic late reciprocal relationship of the RS-T segments and T-waves in Leads I and III together with a typical Q_3 pattern, suggests that pericarditis even with effusion does not appreciably alter the electrocardiographic pattern induced by acute coronary occlusion if the infarction is in the posterior basal portion of the ventricle.

The electrocardiographic pattern in this case, however, need not be taken to controvert the above conclusions of Barnes [11] for of the eight cases studied by that author seven were eventually shown to have anterior or apical infarction in the left ventricle, and the remaining case suggesting posterior basal infarction did not show exactly typical changes in the electrocardiogram, and may have been an instance of combined posterior and anterior infarction of the left ventricle, as pointed out by the author, since no friction rub was heard and autopsy was lacking. It is quite likely in view of the foregoing, that the electrocardiographic pattern noted by Barnes is typical only of anterior or apical infarction in the left ventricle complicated by pericarditis, and it may eventually be shown in additional cases that the characteristic electrocardiographic pattern of infarction of the posterior basal portion of the left ventricle is not overshadowed by the advent of pericarditis.

Summary

A case of acute coronary thrombosis with massive pericardial effusion necessitating paracentesis has been described. This case was further complicated by adeno-carcinoma of the cecum found during convalescence and later resected successfully.

The electrocardiographic signs of pericarditis, including *pericarditis epistenocardica,* have been briefly reviewed. The study of serial electrocardiograms taken in the present case suggests that when infarction of the posterior basal portion of the left ventricle is complicated by pericarditis, the electrocardiographic signs of this complication will be lacking, in contra-distinction to the electrocardiographic pattern observed when pericarditis follows infarction of the anterior or apical portion of the left ventricle.

Note: When preparing this report I overlooked the article of Wolferth and Wood (Arch. Int. Med., 1935, lvi, 77) in which they showed that electrocardiograms similar to those depicted by Barnes may be due to infarction involving both the anterior and posterior surfaces of the left ventricle.

Recently Vanderveer and Norris (Am. Heart Jr., 1937, xiv, 31) have adduced evidence that the electrocardiographic changes in pericarditis are the result of superficial myocarditis associated with the pericarditis.

The patient described in this case report is free from all complaint at present, three years after the onset of his attack. His electrocardiogram shows no change from the last one illustrated.

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HYPERINSULINISM ASSOCIATED WITH HYPOTHYROIDISM: TWO CASE REPORTS *

By JOHN L. CARMICHAEL, M.D., *Birmingham, Alabama*

THE following cases are reported because the findings indicate that there may be a cause and effect relationship between hypothyroidism and hyperinsulinism, or at least that hypothyroidism may aggravate hyperinsulinism. Considerable experimental work has indicated a definite interrelationship between the secretion of the thyroid and that of the islet portion of the pancreas. It has been shown also clinically, that the injection of insulin changes the basal metabolic rate, but in a review of the literature available to us, no case report has been found indicating a definite relationship between hyperinsulinism and hypothyroidism. Tedstrom,[1] however, reports a case with a hyperinsulinism type of blood sugar curve in which the basal metabolism reading was minus 22. He states that the basal metabolic rate was increased to normal with thyroid extract without relieving any symptoms except that of headaches. He does not indicate, however, that the glucose tolerance test was repeated while the metabolism was at a normal rate.

Marine [2] reports Falta as believing that the thyroid and pancreas are antagonistic. Falta found that thyroidectomized dogs were less sensitive to the hyperglycemic action of epinephrine than normal animals. This, so Marine states,

* Received for publication May 29, 1937.

has been confirmed by Bodansky and by Burns and Marks. Bodansky reported that thyroidectomized sheep were more sensitive to insulin than normal animals. Marine also is authority for the statement that thyroid or thyroxine fed to thyroidectomized rabbits decreases the hypoglycemic action of insulin.

Simnitzky and Komendantowa [3] by rather extensive histological studies on animals found that the continued injection of insulin produces a diminution of the function of the thyroid which manifests itself morphologically in the flattening of the epithelium lining the walls of the acini and in a retention of the colloid in the acini.

Ernst and Kaufman [4] gave one gram of dextrose per kilogram of body weight to 11 patients suffering from various diseases. They then gave one-fifteenth of a unit of insulin per kilogram of body weight to each patient and recorded blood sugar readings at 20 minute intervals.

After the ingestion of the dextrose and the injection of insulin the average increase of blood sugar reading was as follows: After 20 minutes 34.7; after 40 minutes 45.5; after 60 minutes 44; and after 80 minutes 38.7. The same procedure carried out on a small group of patients suffering from Basedow's disease and from hyperthyroidism gave the following average increases in blood sugar readings: After 20 minutes 41.1; after 40 minutes 51.7; after 60 minutes 54.4; and after 80 minutes 47.6. This clinical experimental work, as will be observed, indicates that increased activity of the thyroid inhibits to some extent the action of insulin so that the blood sugar rises higher after dextrose is given in the hyperthyroid and exophthalmic goiter cases than in those whose thyroid function is less active.

These latter observations are also in accordance with the observations of those clinicians who have noted that in cases of diabetes associated with hyperthyroidism the surgical treatment of the hyperthyroidism lessens the severity of the diabetes. Apparently the removal of an excess of thyroid secretion allows the production of more insulin.

The following cases add further evidence tending to substantiate the observations outlined above and suggest a treatment for some cases of hyperinsulinism other than diet and surgery.

Case Reports

Case 1. E. C. H., white, male, aged 36, a bookkeeper, was admitted to the Birmingham Baptist Hospital on December 25, 1935, and was first seen by me shortly afterward. His wife gave the history that she had been awakened about 3:00 a.m. and had found the patient in a convulsion during which he foamed at the mouth and bit his tongue to the extent that the froth was quite bloody. He was unconscious for about 30 minutes after she awakened, but seemed normal after consciousness returned. He was admitted to the hospital about one-half hour after regaining consciousness.

When I first saw him, a few minutes after his admission, he was rational and comfortable except for a slight headache. He did not recall anything immediately preceding the convulsion. Physical examination revealed a well developed and well nourished young man apparently relaxed and comfortable in bed. He was well oriented. Nothing abnormal on physical examination was found except a swollen and slightly lacerated tongue. Pupils were equal and symmetrical and responded to light. Patellar, biceps and abdominal reflexes were normal. The Babinski sign was not present.

Past history was irrelevant except that he had awakened one morning several weeks before with a sore and swollen tongue. He also stated that he had great difficulty keeping awake at times and had, on one occasion, fallen asleep while driving his car.

His family history was irrelevant except that one sister had diabetes and one niece had exophthalmic goiter.

Routine laboratory examination on admission was negative. A spinal puncture was done some hours after admission. This revealed the spinal fluid under normal pressure. Seven cells were found per cubic millimeter and there was a trace of

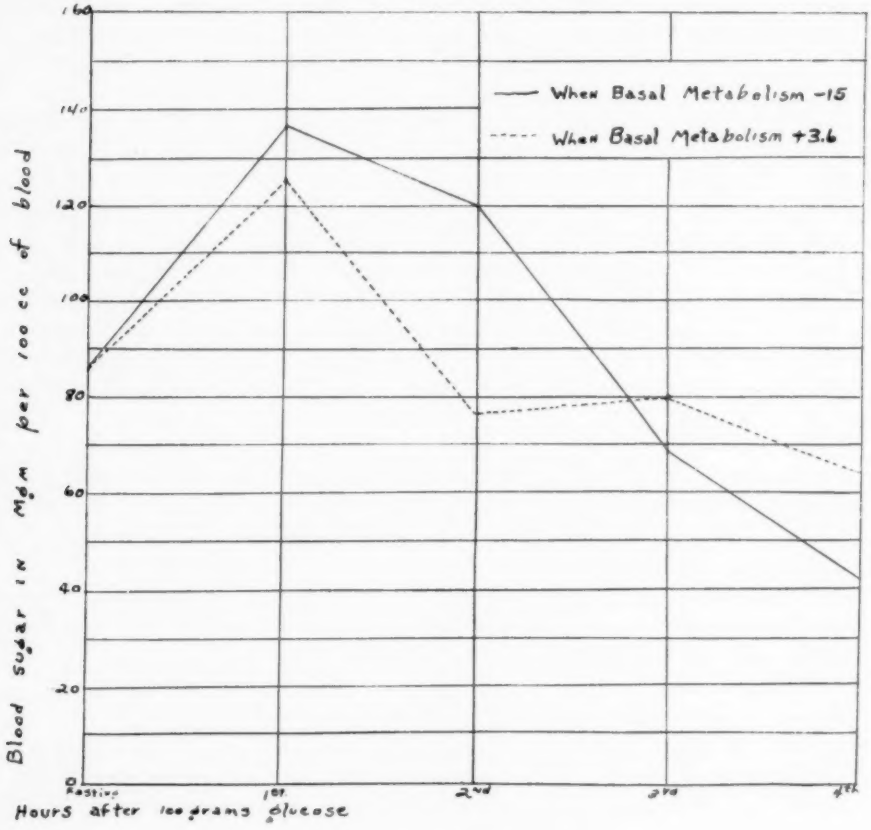

FIG. 1. Case 1.

globulin. The Wassermann was negative. A fasting blood sugar determination a few hours after his admission was 108 mg. per 100 c.c. of blood.

A few days later a glucose tolerance test was done. After a redetermination of the fasting blood sugar the patient ingested 100 grams of glucose and hourly blood sugar readings were taken for four hours. His fasting blood sugar was 87 mg. per 100 c.c.; after one hour it was 137; after two hours 120; after three hours 68; and after four hours 42, as shown in figure 1. A basal metabolic reading taken immediately before the ingestion of glucose gave on two tests minus 15 each time. The patient was put on three grains of desiccated thyroid gland which he took daily, with

rest intervals, until four and one-half months later. The basal metabolism reading at this time was plus 3.6. A glucose tolerance test on the following day gave the following results, as shown in figure 1. The fasting blood sugar was 87 mg. per 100 c.c.; after one hour 127; after two hours 77; after three hours 80; and after four hours 75. This suggests that the increased utilization of thyroid secretion in the body had depressed the production of insulin so that the blood sugar had remained higher and thereby prevented further convulsions. Until this date the patient has had no further convulsions.

Case 2. C. V., white, male, aged 39, locomotive fireman, was seen at the office on June 30, 1936. His chief complaint was of recurring attacks of convulsive seizures which were accompanied by loss of consciousness. The first one had occurred on July 27, 1935. The attacks, he stated, usually started with twitching of the muscles of the right side of the face and a bending of the body over to the right side. They were preceded by cold chills up and down the spine and a feeling of lightness in the head. He had noticed that the attacks had always occurred when he had gone without food for an unusually long time. His friends had told him that the convulsive twitching became generalized over his body and that he would remain unconscious for 10 or 15 minutes. He states that for 20 or so additional minutes he would be disoriented and unable to talk. There had been probably 15 or 20 such attacks before the consultation on June 30, 1936. The last one had occurred five days previous to his visit to the office. He stated that in addition to those attacks he had had a rather marked loss of memory for recent events. Past history and family history were irrelevant except that his father had been excessively overweight.

Physical examination at this time revealed a well developed and overweight white male, 66½ inches in height and weighing 234 pounds. Nothing else abnormal was found on physical examination. The laboratory examination including a fasting blood sugar was normal except that the basal metabolism reading was minus 20. A glucose tolerance test, however, gave the following results: Fasting blood sugar 85 mg. per cent; first hour after 100 grams of glucose 128; second hour 112; third hour 55; and fourth hour 56 mg. per 100 c.c. of blood. It will be noted that a low of 55 mg. per 100 c.c. of blood occurred three hours after the ingestion of the glucose.

Experience with the previous case caused us to try to control the hyperinsulinism by increasing the metabolic reading to normal with thyroid extract. Accordingly we put this patient on four grains of thyroid daily. On July 23 the basal metabolism reading was minus 3.8. At this time the glucose tolerance test was repeated with results as follows, as shown in figure 2: Fasting blood sugar 92, first hour after glucose 174; second hour 124; third hour 84; fourth hour 80; fifth hour 88; and sixth hour 92 mg. per 100 c.c. of blood. The patient had continued to have occasional attacks so we increased the thyroid dosage to 5 grains daily and on August 12, about three weeks later, we repeated the basal metabolism reading and the glucose tolerance test. The basal metabolism reading was plus 7.5 and the glucose tolerance test was as follows (figure 2): Fasting blood sugar 92; first hour after glucose 184; second hour 141; third hour 95; fourth hour 65; fifth hour 78, and sixth hour 90 mg. per 100 c.c. of blood.

In spite of this change in glucose tolerance the patient reported that he was having still occasional attacks of the same type of convulsive seizure. They were, however, not so numerous and he felt much better than he had felt previously.

We had allowed him to manage his diet as he chose. We inquired of him what his diet was and he explained that he had been visiting with friends and relatives and eating a great deal of pies and cakes and other carbohydrates. We felt, however, now that we would not be able entirely to control the attacks with thyroid extract. We therefore placed him on a high fat and low carbohydrate diet, as has been sug-

gested by Harris.[5] This he has followed now for about two and one-half months with only one such attack. We obtained the history in regard to this attack that he had eaten a heavy meal one evening and had taken a purgative that evening and the morning after. The attack occurred at the noonday meal the day following the indiscretion in diet. A further follow-up on this case indicates that he still has an occasional attack.

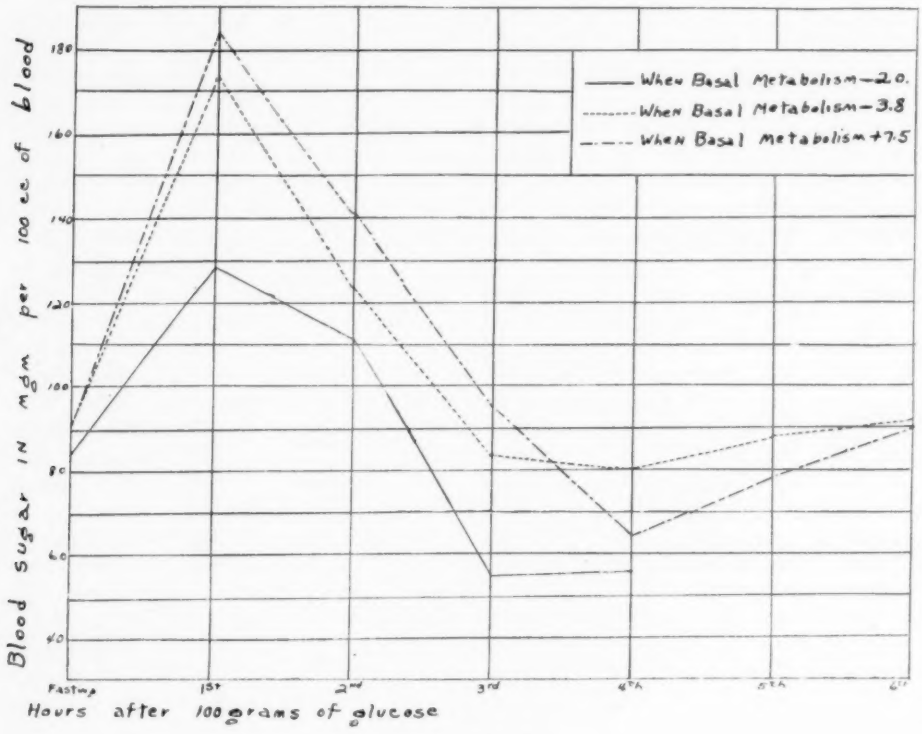

FIG. 2. Case 2.

SUMMARY

1. The literature is briefly reviewed and an indication of mutual antagonism between the thyroid and islet secretions is noted. No attempt is made to determine whether the antagonism is direct or through the intermediary of some gland such as the pituitary.

2. Case reports of hyperinsulinism associated with hypothyroidism are given.

3. The effect on the hyperinsulinism curve of the feeding of desiccated thyroid is noted. Further progress of the cases under thyroid medication is given. This follow-up indicates that some cases of hyperinsulinism may be improved if not held entirely in check by the use of desiccated thyroid gland. It is realized, however, that results of such treatment in a large number of cases followed over a much longer period of time would be necessary before any trustworthy conclusions could be drawn.

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MUSCULO-SPIRAL PARALYSIS AFTER SERUM INJECTION (RECURRING AFTER SECOND INJECTION) *

By Leopold Brahdy, *New York, N. Y.*

L. D., a hospital orderly 25 years of age, was using alcohol in excess. He had never been in any occupation which could have exposed him to lead. On February 24, 1934, he was given 1500 units of tetanus anti-toxin because of a laceration of the sole of the foot. One week later, he complained of severe pain in the neck and in both arms. Examination showed the muscles of the arms tender and in some degree of spasm. The diagnosis of polyneuritis was made. On April 3, examination showed left wrist drop; no anesthesia. The wrist drop persisted several months and finally disappeared, leaving no residual signs or symptoms. In August 1934, he was admitted to the hospital for two days for acute alcoholism. No abnormality of the extremities was noted at that time.

In 1934, he had a lobar pneumonia. No serum was used and he made an uneventful recovery.

On August 22, 1935 he was pinched over the dorsum of the elbow by a patient suffering from cerebro-spinal meningitis. There was no open wound. However, another orderly (J. G.) had been scratched by this same patient several days before and had developed gas bacillus infection from the scratch. This fact frightened L. D. and he requested and was given "1500 units of tetanus anti-toxin and a prophylactic dose of gas gangrene bacillus" serum. This injection was given subcutaneously in the left upper arm. He is quite certain that there was no intramuscular injection. He had no symptoms until eight hours later when he developed pains in the left arm radiating from the spine to the fingers. Two days later, he noticed left wrist drop. There was no urticaria nor any other anaphylactic symptoms. Physiotherapy treatments were administered for several months, but the wrist drop persisted.

Since the patient is well acquainted with medical procedures, his statement that the injection was subcutaneous is more reliable than would be that of another layman. In spite of that history, we considered the possibility of direct nerve injury. The absence of any pain, weakness or numbness, however, until eight hours after injury, was entirely inconsistent with this hypothesis.

In November 1935, he was readmitted for three days for acute alcoholism.

* Received for publication May 13, 1937.

Twenty months after the onset of the second wrist drop, examination by Dr. Byron T. Stookey at the Neurological Institute was reported in part, as follows:

"The neurological examination is entirely negative except for the presence of rather lively but equal reflexes of both lower extremities and the right upper. The left upper reflexes, supplied by the seventh cervical, namely, the triceps and the ulnar, are diminished. The ulnar jerk is absent on the left side and is present on the right. There is definite atrophy of the extensors of the fingers of the left hand. The *supinator longus* contracts, as does also the *brachia radialis longus* and *brevis*, but there is no extension of the fingers or of the thumb. In short, this patient has evidence of a wrist drop which has in part recovered sufficiently to permit part extension of the wrist but no recovery has taken place in the extensors of the fingers or the thumb."

In 1932, Wilson and Hadden [1] reviewed cases of peripheral nerve lesions after serum injection, and in 1933 Wulf [2] reported nerve lesions after serum injection. There is no case reported of transient paralysis with recurrence of the paralysis in the same nerve after a second injection. We have here a case of paralysis (now permanent) recurring after a second injection. Excessive alcoholism may have rendered the peripheral nerves susceptible. Although I have seen many hundreds of patients who had prophylactic or therapeutic serum injections, this is the only one resulting in any permanent defect. I believe that we may accept Wulf's statement to the effect that disturbance of the nervous system is so rare that it does not limit the indications for the use of serum.

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EDITORIAL

THE PRESIDENTIAL ADDRESS

THE Presidential address of Dr. James Howard Means at the Convocation of the College attracted unusual attention. The membership of the College will have the opportunity of reading the full text of this able speech in the May issue of the ANNALS. However, because of the misinterpretation of certain of Dr. Means' remarks it has seemed advisable to the Regents that in this issue there should appear a statement addressed to the membership of the College and to the general medical profession.

In some quarters it was apparently thought that Dr. Means had called upon the medical profession to revolt against the leadership of the American Medical Association. Indeed, it was suggested that under certain conditions the College should take away from the American Medical Association the function of representing the medical profession. Naturally such statements have not failed to be disturbing to those of our Fellows who did not hear Dr. Means' address.

In his remarks Dr. Means was critical of the recent policy of the American Medical Association which he summarized as standpatism. He expressed himself as believing that since the organization of the American Medical Association is that of a democracy it would be in a healthier state if it always contained, in addition to the existing administration, an effective opposition party so that there might be active discussion of vital issues. He felt that it was desirable that those who believe in popular government should bestir themselves to bring this about.

It is no more a revolt against the American Medical Association to criticize its present policy and to suggest that within its membership an effective opposition should be organized, than it is revolt against the United States for one of its citizens to criticize the New Deal and to express a fervent wish for a successful opposition party.

Dr. Means made it very plain that he was not giving voice to a policy, nor to a political program of the College, for in his analysis of the purpose of a college of physicians he stated his opinion as follows: "I have said what I have said in order to indicate what I conceive to be the fundamental difference between a college of physicians and a national or state medical society. Each has its use but they are different. The college is not in competition with the medical association. The college should be a counterpart of the university, not that of the state. It should be as unthinkable for us to have a College policy regarding social, economic, political or scientific aspects of medicine as for one of our universities to take sides in a political campaign. It should also be unthinkable that we should at any time be unwilling to hear all sides of any problem related to the practice of medicine."

It is evident therefore that Dr. Means, believing as he does that the College should be a body without a policy, was expressing only personal views concerning the advisability of an opposition party in the American Medical Association; and least of all was he presaging a future supplanting of the Association by the College.

The interpretations to which we have referred are therefore quite unwarranted by the content of Dr. Means' speech.

Because of the questions raised by this incident the following account of the position taken by the Officers and Regents of the College in the past may be of interest.

Among the Objects of the College mentioned in the Constitution (Article III, Sec. 1a) is that of "maintaining and advancing the highest possible standards in medical education, medical practice and clinical research." Since the Officers and Regents are empowered to represent and to act for the College in matters defined in the Constitution and the By-Laws the above section would permit the Officers and Regents by formal motion recorded in their minutes to commit the College to any policy or action which in their opinion would further these objects. However, up to this time the conception of the proper rôle for the College has been in accord with Dr. Means' definition. The College has not felt that it should have any policy other than that of the ethical principles embodied in its Fellowship Pledge. It has so far followed a precedent of holding aloof from any official action, or pronouncement of opinion bearing upon disputed questions of medical practice. It has become customary to refer inquiries, requests for opinions, etc. on such matters to the Committee on Public Relations who submit a report to the Board of Regents. The Board of Regents has up to this time consistently stated that the College was not committed to any policy and that its function was not that of serving as an arbiter. It seems highly probable that this precedent will continue in force. It seems certain, moreover, that should some future emergency in the affairs of the medical profession induce the Officers and the Regents of the College to attempt to marshall the strength of its membership in defense of some vital principle, a first step, before pronouncing a College policy in any contentious question, would be to submit the proposal to the vote of the Fellows of the College in a General Meeting.

The College has been and is unreservedly devoted to the principle of free speech. The more vital and the more controversial a topic is, the more important it is that the members of the College should hear the best obtainable presentation of both sides. The College will keep its meetings open to the expression of any sincere opinion upon any side of any medical problem. Nor does the College intend to taboo any subject from discussion by its own Fellows, Masters, Governors, Regents or Officers.

It should be plain to the membership, however, that no statement by any one of these constitutes a College policy.

REVIEWS

Arteriovenous Aneurysm. By EMILE HOLMAN, M.D. 244 pages; 15 × 22 cm. The Macmillan Co., New York. 1937. Price, $5.00.

This recent book by Holman justly deserved the recognition given when it was awarded the Samuel D. Gross prize by the Philadelphia Academy of Surgeons. The first part of the book deals with experimental work and if studied carefully yields clearer understanding of the physiological adjustments to the presence of arteriovenous fistulae. The author then discusses in detail both congenital and acquired arteriovenous fistulae and aneurysms of the extremities and other parts of the body. This portion of the book is a most excellent summary of recent clinical investigations of these conditions.

The book on the whole is a splendid piece of work from the experimental, clinical and historical points of view. It will prove to be of value to the teacher, both of medicine and of surgery, and especially to the research worker in this field.

T. B. A.

Radiation Therapy. By IRA I. KAPLAN. 558 pages; 16 × 24 cm. Oxford University Press, New York. 1937. Price, $10.00.

This volume will be of interest to the internists as well as to those treating disease by means of radium and roentgen-rays. It is written from a practical viewpoint. Dr. Kaplan's wide experience in radiation therapy is evident in every chapter. The chapter on physics by Braestrup is unusually clear so as to be readily understandable to any physician. The illustrations are excellent and the extensive bibliography will be helpful to students. The subject cannot be fully covered in one volume and certain chapters, notably those on radiation therapy in neurological disease, inflammatory processes and bone diseases, seem too brief to be adequate. It can be recommended as an excellent reference on radiotherapy.

W. L. K.

Medical Greek and Latin at a Glance. By WALTER R. AGARD. Second edition revised. 87 pages; 16 × 25 cm. Paul B. Hoeber, Inc., New York. 1937. Price, $1.50.

This little volume will prove of real help in understanding many of the terms in our bilingual medical nomenclature. It is really a glossary and makes plain the derivation and meaning of many words to those who have little Latin and less Greek. It meets a real need.

L. A. M. K.

Essentials of Psychiatry. By GEORGE W. HENRY, M.D., Associate Professor of Psychiatry, Cornell University Medical College, New York City. 465 pages; 15 × 24 cm. The Williams and Wilkins Company, Baltimore. 1938. Price, $5.00.

This is the third edition of a very well known book, which has gained popularity because it presents the essentials of psychiatry in understandable language. This specialty has made rapid progress, and Dr. Henry has brought his book up to date.

In his twenty chapters the author has steadfastly held to his conclusion that psychiatry is as scientific as any other branch of medicine, and that in its practice it is necessary for the physician to take all of the facts regarding illness into consideration. "There is no short road to the understanding of human reactions and it is

only after years of training and experience that the physician is prepared to deal adequately with personality disorders."

The first ten chapters discuss the development of the personality and its disorders. Dr. Henry clearly describes the various types of psychopathology, discussing each classification in the following order: definition, frequency, causes, symptoms, types, course of illness, prognosis, excerpts from illustrative cases, and discussion of the classification.

The last ten chapters take up: method and purpose of mental examination, principles of treatment, psychiatric nursing, psychopathology of the normal, mental hygiene, disorders of childhood, psychiatric social service, medico-legal aspects, psychiatric history, and milestones in psychiatric history.

J. L. McC.

Practical Talks on Kidney Disease. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University School of Medicine. 176 pages; 14.5 × 22 cm. Charles C. Thomas, Springfield and Baltimore. 1937. Price, $3.00.

This small volume makes no pretentions to being an exhaustive treatise on the subject of renal disease. The title is well chosen. Nevertheless, it contains the essential information presented in a readable fashion. There are brief chapters on the physiology of the kidney, impairment of renal function, and tests of renal function. The author then presents the principal signs and symptoms of renal disease and devotes short chapters to the more important ones such as edema, albuminuria, hypertension, retinal lesions (illustrated), etc. The various clinical syndromes and their treatment are then described. Part VII deals with hypertension and the rôle it may play in kidney disease.

Those who have made a particular study of this field probably will gain nothing new from this book. The reviewer recommends it to practitioners and students.

W. S. L., JR.

Physical Diagnosis. By RALPH MAJOR, M.D., Professor of Medicine in the University of Kansas. 457 pages; 15.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1937. Price, $5.00.

This textbook is a comprehensive survey of physical diagnosis. It includes chapters on all parts and all systems of the body, with two additional, one on pain and the other on history taking.

Dr. Major includes so much information, with so many interesting and important little details, that the result is at times confusing. This is obviated to a certain extent by the splendid illustrations, both photographs and diagrams, which help to elucidate the text.

Those interested in Dr. Major's former book; "Classic Descriptions of Disease," will be pleased to know that the subject is approached as much as is possible from an historical point of view. Besides the introductory chapter, with its accounts of some of the great personages in medicine, the text includes many original descriptions of disease and some original illustrations.

The clinical side of physical diagnosis is stressed, but one wishes that a little more space had been given to those chapters dealing with diseases of the heart and lungs. The chapter on the pulse, however, is excellent and, but for the omission of any mention of auricular flutter, might serve as a standard for instructors in physical diagnosis.

The usefulness of the book is enhanced by the splendid bibliographies that the author has appended to each chapter.

R. A. R.

Alcohol: One Man's Meat. By EDWARD A. STRECKER, M.D., and FRANCIS T. CHAMBERS, JR., M.D. 230 pages; 14 × 21 cm. Macmillan Co., New York. 1938. Price, $2.50.

This volume dealing with "Another Man's Poison" constitutes an excellent graduate course on how to handle chronic alcoholics. From cover to cover it is packed with interesting information concerning the physiology and toxicology of alcohol, the psychology and pseudo-philosophy of the alcoholic patient and the ways and means for the intensive psychical reëducation of the victim of alcoholism. No thinking physician can read it without deepening his understanding of the problems of alcoholism and increasing his ability to cope with them, for the treatment suggested is directed not so much to the disease itself as to its underlying causes.

The authors question the stimulating action of alcohol and regard its effect rather as that of a camouflaged narcotic, the deception of stimulation arising from the release of the lower nerve centers from the control of the higher by its narcotizing power. Alcohol is used commonly by the laity because it is the only narcotic that can be purchased inexpensively in a glass or bottle and without a doctor's prescription. It is used as a salve to the ego as, in the beginning at least, it acts magically in soothing the painful wounds of personal belittlements and feelings of insignificance.

The authors differentiate normal from abnormal drinkers. The normal drinker uses alcohol in moderate amounts as a socially accepted gesture and for purposes of conviviality and rarely gets into trouble from it. Through its use the adult attains temporarily a childlike state of mind and freedom from the behaviorism demanded by maturity. Such a one drinks to exaggerate reality because he finds reality enjoyable. The border line between normal and abnormal drinking is crossed when alcohol is used as an aid in the adjustment to reality. The abnormal drinker is the individual who cannot face reality without alcohol, but whose adequate adjustment to reality is impossible as long as he uses alcohol. In other words the abnormal drinker is an abnormal individual seeking release from reality through the medium of alcohol. Treatment of alcoholism therefore involves the management of an abnormal personality. The authors take their cues for treatment from the psychotherapists who have led their neurotic patients suffering from neurasthenia, anxiety states, hysteria or compulsive neuroses back to the normal planes of life. Many of the procedures used in these various disturbed psychical states are equally effective in the management of the chronic alcoholic.

The authors believe that the psychoneurosis which is responsible for much of our alcoholism must be traced back to its causes and these must be met by appropriate psychotherapy. The underlying neuroses are due most frequently to unfavorable early home life, constitutional predisposition, or to chronic disease, sex conflicts, financial difficulties, restricted outlets or actual mental defects.

According to the authors, treatment should not be started while the patient is still drinking, in fact not until the patient sees his own need, seeks help on his own initiative without outside persuasion or coercion, and is willing and eager to participate in his own cure. The psychotherapist should not undertake treatment until he is convinced that it is possible to bring about a state of mind in his patient that desires not to drink any more. The patient must understand in the beginning that it is impossible for him ever to learn to drink in moderation. He must be willing to face life without alcohol. The treatment advised, consists of prescribed rules and schedules, psychological treatments, mental reëducation and physical adjustments. The patient must be carried from lower to higher and mature levels, must be taught his own needs, gain an insight into his crippled condition and taught how to help to cure himself. He must practice abstinence throughout the period of management. The treatment usually necessitates at least one year of supervision and in all about one hundred conferences with the psychotherapist.

The reviewer believes that this book constitutes a real contribution to medicine. The treatment as outlined seems ideal for the more intelligent and tractable alcoholics, especially if enthusiastically applied by a properly qualified psychotherapist. Whether or not this or any other system of treatment will meet the needs of the average and less intelligent drunkard is open to question. Certainly it would not appear to be more costly or time consuming than present methods of management which entail long or frequent and intermittent hospitalization.

L. G. R.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. John S. Chambers (Fellow), Lexington, Ky.—"The Conquest of Cholera";
The American Foundation Studies in Government—Volumes I and II, "American Medicine: Expert Testimony Out of Court."

Reprints

Dr. Alonzo F. Brand (Fellow), Fayetteville, N. Y.—one reprint;
Dr. Charles H. Cocke (Fellow), Asheville, N. C.—seventeen reprints;
Dr. A. R. Foss (Fellow), Missoula, Mont.—one reprint;
Col. S. W. French (Fellow), M.C., U. S. Army—one reprint;
Dr. P. A. Gray (Fellow), Santa Barbara, Calif.—one reprint;
Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind.—five reprints;
Dr. Abel Levitt (Fellow), Buffalo, N. Y.—one reprint;
Dr. C. F. Morsman (Fellow), Hot Springs, S. D.—two reprints;
Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—one reprint;
Dr. Aaron E. Parsonnet (Fellow), Newark, N. J.—one reprint;
Dr. Lee Roy Woodward (Fellow), Mason City, Iowa—one reprint;
Dr. Paul A. Draper (Associate), Colorado Springs, Colo.—two reprints;
Dr. Arthur O. Hecker (Associate), Polk, Pa.—three reprints;
Dr. David W. Kramer (Associate), Philadelphia, Pa.—ten reprints;
Dr. Charles E. Lyght (Associate), Northfield, Minn.—one reprint;
Dr. Matthew Molitch (Associate), Philadelphia, Pa.—twenty-nine reprints;
Dr. Eugene S. Sugg (Associate), New York, N. Y.—one reprint.

Regional Meeting of Kansas Members

Members of the American College of Physicians resident in the State of Kansas held their annual meeting and dinner in Wichita, under the Governorship of Dr. Thomas T. Holt, February 22, 1938. The following program was rendered:

"Treatment of Cardiacs with Oscillator Bed," Dr. Harold H. Jones (Fellow), Winfield, Kan.;
"Medical Problems in Mineral Metabolism," Dr. Frances Helen Schiltz (Fellow), Wichita, Kan.;
"Peptic Ulcer, Carcinoma Question," Dr. H. N. Tihen (Fellow), Wichita, Kan.;
"Use of Insulin in Mental Disease," Dr. D. V. Conwell (Associate), Halstead, Kan.;
"Insulin in Treatment of Schizophrenia," Dr. R. M. Fellows (Fellow), Osawatomie, Kan.;
"Cerebral Spinal Pressure Relative to Blood and Circulatory Disturbance," Dr. Thomas T. Holt (Fellow and Governor for the State of Kansas), Wichita, Kan.;
"Simmond's Disease (Pituitary Cachexia)," Dr. G. F. Corrigan (Associate), Wichita, Kan.;
"Clinical Phases of Recent Developments in Connection with the More Modern Developments in Cancer Etiology," Dr. P. M. Krall (Associate), Kansas City, Kan.

Dr. E. J. G. Beardsley (Fellow and Governor for Eastern Pennsylvania), Philadelphia, Pa., spoke on "Medical Conditions Which Simulate Abdominal Emergencies" at the University of North Carolina's Postgraduate Seminar, held at High Point, N. C., March 17, 1938.

Dr. Beardsley also held a morning and afternoon medical clinic at the Sacred Heart Hospital, Allentown, Pa., on March 24, 1938.

Dr. Claude Ellis Forkner (Fellow), who has just completed a five-year appointment as Associate Professor of Medicine in the Peking Union Medical College, has returned to New York and has been appointed Assistant Professor of Clinical Medicine at Cornell Medical School. Dr. Forkner has also been appointed Assistant Attending Physician at the New York Hospital, and has opened an office for the practice of Internal Medicine and Hematology at 121 East 60th Street, New York, N. Y.

Dr. Paul H. Ringer (Fellow), Asheville, N. C., has been made President of the Southern Tuberculosis Conference.

Dr. Charles S. Holbrook (Fellow), New Orleans, La., has been made President-Elect of the Southern Psychiatric Association.

Dr. Paul D. White (Fellow), Boston, Mass., addressed the North Side Branch of the Chicago Medical Society, recently, on "Nature, Diagnosis and Treatment of Heart Disease."

The second annual New Orleans Graduate Medical Assembly was held in New Orleans, March 7 to 10. Fellows of the College who participated on the program were Dr. Reginald Fitz, Boston, and Dr. Udo J. Wile, Ann Arbor, Mich.

The tenth annual spring clinical conference of the Dallas Southern Clinical Society was held at Dallas, Tex., March 14 to 17. Guest speakers and their subjects were Dr. Russell L. Haden (Fellow), Cleveland, Ohio, "Treatment of Arthritis," and Dr. Howard T. Karsner (Fellow), Cleveland, Ohio, "Research on Hypertension."

Dr. Walter P. Gardner (Fellow), Hastings, Minn., has been made Superintendent of the Anoka State Hospital.

Dr. Wallace M. Yater (Fellow and Governor for the District of Columbia), Professor of Medicine, Georgetown University School of Medicine, Washington, D. C., delivered the annual Kober Lecture at the University March 28. His subject was "Goiter and the Heart: An Exposition of the Present Status of Our Knowledge of the Subject, Including Original Research Work in This Field."

Dr. Carl J. Wiggers (Fellow), Cleveland, Ohio, spoke on "The Dynamics of Hypertension" before the annual meeting of the Federation of American Societies for Experimental Biology, held at the Lord Baltimore Hotel, Baltimore, Md., March 30 to April 2.

Dr. Felix J. Underwood (Fellow), Jackson, Miss., has been appointed a member of the Rockefeller Foundation Board to serve for a period of three years. This Board is composed of six members and decides the policy of the Foundation throughout the world.

Recent changes at the University of Colorado School of Medicine, Denver, include the following:

Dr. Philip Work (Fellow), to Professor of Neurology and head of the department; Dr. Constantine F. Kemper (Fellow), Associate Professor of Medicine; Dr. Harry Gauss (Fellow), Assistant Professor of Medicine.

Dr. Rollin H. Stevens (Fellow), Detroit, was guest of honor at a dinner January 28 given by the staff of Grace Hospital, the Detroit Roentgen Ray and Radium Society and the Detroit Dermatological Society, in observance of his seventieth birthday. Among other gifts Dr. Stevens received a leather bound copy of the January issue of "Radiology," which was dedicated to him. Each guest received a reprint of the opening article in the journal, entitled "Rollin Howard Stevens, An Anniversary Chronicle of His Useful Life," by Dr. Percy Brown (Fellow), of Boston.

Dr. George R. Minot (Fellow), Boston, delivered a lecture January 20 at the Mayo Clinic, Rochester, Minn., on "Some Aspects of the Etiology, Diagnosis and Treatment of Anemia."

Dr. Eugene M. Landis (Fellow), Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, delivered the annual N. W. Jones Lectures at the University of Oregon Medical School, Portland, February 9 to 10. Dr. Landis spoke on "Capillary Pressure, Capillary Permeability and the Movement of Fluid Through the Capillary Wall" and "The Effects of Pressor Drugs and Kidney Extracts on Blood Pressure and Peripheral Blood Flow."

The Neuropsychiatric Society of Virginia held its first meeting for 1938 at the University Hospital on January 26. Papers were presented by Dr. D. C. Wilson (Fellow) and Dr. Dudley C. Smith (Fellow), University, Va.

At the February meeting of the New York Polyclinic Medical School and Hospital Clinical Society, Dr. Lea A. Riely (Fellow and Governor for the State of Oklahoma) spoke on "Modern Concepts of Addisonian or Macrocytic Anemia."

Dr. Albert Soiland (Fellow), Los Angeles, has been recently elected National President of the United States Naval Reserve Officers Association. Dr. Soiland is a Trustee of the Pan-American Medical Association and attended the 7th Congress Cruise during the course of which he contributed three papers to the program.

Dr. Joseph H. Barach (Fellow), Pittsburgh, Pa., addressed the Allegheny-Garrett County Medical Societies at Cumberland, Maryland, on February 25, 1938. His subject was "Science of Nutrition and the Treatment of Diabetes."

Dr. Walter A. Bastedo (Fellow) addressed the Wayne County Medical Society in Detroit, Mich., on March 7, on "Therapeutics and the Physician's Prescription." He has been the recipient of the "Diploma de Honor" of Venezuela Farmaceutica, which governs the standards of drugs in Venezuela.

Dr. Erwin E. Mayer (Fellow), Baltimore, Maryland, addressed the "Association of Dental Surgeons" on March 23, 1938, on "Oral Infections from the Internist's Viewpoint."

OBITUARIES

DR. THOMAS BARNES FUTCHER

Thomas Barnes Futcher (Fellow) was born January 1, 1871, in St. Thomas, Ontario, Canada, and died February 25, 1938, in Baltimore, Maryland. His early years were spent at home attending the local schools and at the age of 19 he entered the University of Toronto where in 1893 he received the degree of Bachelor of Medicine with high honors. After a year as house officer in the Toronto General Hospital, he went to Johns Hopkins to be a member of the House Staff under his fellow Canadian, Dr. William Osler. Seven years were spent in the Hospital, the last three as Resident Physician on the Medical Service. He then entered consultation practice in Baltimore opening an office next door to the home of his beloved chief, Dr. Osler. In 1909 he married Gwendolyn Marjory Howard of Toronto who was a daughter of the famous Canadian, Dr. Robert Palmer Howard, to whom Dr. Osler owed so much of his early medical inspiration.

Dr. Futcher's career was one of steady progress in the practice and teaching of medicine. At the time of his death, he was Visiting Physician to the Johns Hopkins Hospital where he was Chairman of the Private Ward Medical Service. He was also Associate Professor of Medicine which is one of the highest academic positions open to part-time teachers at the Johns Hopkins Medical School.

He belonged to many medical societies and in 1931–32 was President of the Association of American Physicians. He was made an Associate of the American College of Physicians in 1925 and became a Fellow in 1930. His interest in the local medical societies was always encouraging; he attended the meetings faithfully, and he was Chairman of the Historical Section of the Baltimore City Medical Society in 1937–38. He was one of the original members of the Interurban Clinical Club and rarely missed the meetings of this Club in other cities.

His medical writings were mostly concerned with metabolic subjects although of his many publications more than half were on such various subjects as haemochromatosis, cancer of the pancreas, erythremia, and disturbances of pituitary function. In Osler's System of Medicine he contributed the sections on Diabetes Mellitus, Diabetes Insipidus and Gout.

Dr. Futcher was a member of a distinguished group of American physicians who continued what Osler began, to balance skillful bed-side observation with the newest laboratory method. He taught, by precept, meticulous care in clinical examination but above all he taught, by example, loyalty to the best medical tradition. His friendship was unfailingly kind—no one can remember his saying anything derogatory about a colleague—and the influence of his quiet, genuinely courteous presence will long be felt.

HENRY M. THOMAS, JR.,
Governor for Maryland.

DR. MICHAEL ANTHONY BURNS

Michael Anthony Burns (Fellow) was born in Philadelphia on May 23, 1884, the son of James M. and Mary A. (Rowen) Burns. After his early education in the parochial schools of Philadelphia and at St. Joseph's College, he entered the Jefferson Medical College from which institution he graduated in 1907.

On the day Dr. Burns began the practice of medicine, following his internship, he entered the neurological service of Dr. Francis X. Dercum, then Professor of Neurology at the Jefferson Medical College. For thirty years, until the beginning of his final illness, he continued in this department in advancing grades as a teacher and, in 1934, his faithful and skilled services were rewarded by election, after the death of Professor Dercum, to the Professorship of Neurology.

During the World War, Dr. Burns was neuropsychiatrist to Base Hospital No. 38 (The Jefferson Medical College Hospital Unit) and, after the Armistice, he was appointed consulting Neuropsychiatrist to the District of Paris. Dr. Burns, at the time of his death, in addition to his teaching and clinical work at the Jefferson Hospital, was Visiting Neurologist to the Philadelphia General Hospital, Neuropsychiatrist to St. Mary's Hospital, Consulting Neurologist to the Wills Eye Hospital, St. Joseph's Hospital and the Shriners' Hospital for Crippled Children.

He was a Fellow of the American College of Physicians and the Philadelphia College of Physicians, a member of the American Neurological and Psychiatric Associations and of the Philadelphia Neurological and Psychiatric Societies.

Dr. Burns was the author of numerous articles on neuropsychiatric subjects and was a frequent contributor to journals specializing upon such presentations.

On October 11, 1910, Dr. Burns married Margaret Agnes Keenan of Philadelphia who, with two sons, Paul V. and John A., survive him.

Dr. Burns was a popular and appreciated physician and his patients will not find it easy to discover another friend and medical counsellor possessing the same happy combination of pleasing and helpful characteristics. Dr. Burns loved life and understood people. In common with all truly successful physicians, he thoroughly enjoyed his professional duties. He worked hard, too hard perhaps, to be able to live long.

Dr. Burns' death on March 7, 1938, due to coronary thrombosis, was a grievous loss to his family and numerous devoted friends and to the medical profession of Philadelphia.

E. J. G. Beardsley, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

ADMIRAL CARY TRAVERS GRAYSON

Admiral Cary Travers Grayson (Associate) was born at Salubria in Culpepper County, Virginia, in 1878 and died in Washington, D. C., on February 15, 1938.

He was educated at William and Mary College (1895–1898) and at the University of The South at Sewanee, Tennessee, where he received his M.D. degree in 1902. He held a degree from the Medical College of Virginia and graduated from the United States Naval Medical School in 1904. He entered the Navy as an Acting Assistant Surgeon in 1903, and was made a Medical Director with the rank of Rear Admiral on August 29, 1916. He was retired from the Navy December 30, 1928. During these years his professional services were eminent and outstanding. He served as personal physician to three presidents, William Howard Taft, Theodore Roosevelt and Woodrow Wilson. He had a combination of knowledge, insight and sympathy which are the necessary attributes of the good physician. His accomplishments from 1928 until the time of his death are a part of our country's history.

Admiral Grayson was a member of the Medical Society of the District of Columbia since January 26, 1916, and an Associate of the American College of Physicians from the inception of the College.

In the death of Admiral Grayson America lost one of her most distinguished citizens. He had devoted most of his life to doing things for other people. The sudden shock of his passing has left sorrow among his many friends and admirers the world over. During his life he inspired friendships such as are granted to few men. Those of us privileged to know him—and the number was legion—can testify to his gallantry and unbounded loyalty. His friends and associates found in him a man in whose personal integrity they could always depend and one in whom trust was never misplaced. He had a keen analytical mind which inspired many to seek his rare good judgment. At the sick bed and in the council chamber his wisdom was particularly manifest and his logical decisions and timely advice were most helpful to his colleagues. His kindly disposition and his unfailing sense of humor saved many a trying situation. He was a gentleman in every sense of the word and his host of friends have suffered an irreparable loss.

In the death of Admiral Cary Travers Grayson, The American College of Physicians has lost one of its most valued and loyal members.

WALTER A. BLOEDORN, M.D., F.A.C.P.,
Washington, D. C.